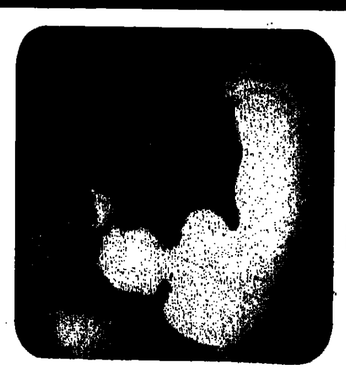
The Upper Functional G.I. Disorder

The Pseudo-ulcer



Ulcer-like symptoms: no G.I. pathology

The patient is convinced it's an ulcer. However, symptoms are not quite typical, and x-ray findings are negative. These findings and the results of additional diagnostic procedures exclude an organic basis for the patient's complaints. A diagnosis of "upper functional gastrointestinal disorder" is made, which is supported by the fact that episodes of painful symptoms coincide with episodes of excessive anxiety, as indicated by the history.

It may be useful to explain to the patient the mechanism by which emotions upset normal G.I. functioning, resulting in hypersecretion and hypermotility and thus causing such symptoms as nausea and epigastric pain. In upper functional gastrointestinal disorders, counseling by the primary physician can often help the patient to understand how excessive anxiety may cause flare-ups of G.I. symptoms.

A disproportionate number of patients seen by the general practitioner suffer from functional disorders, as do more than half of those seen by the gastroenterologist.* Where milder cases may respond to counseling alone, if symptoms are severe and disabling to any degree, a suitable regimen may include medication to reduce the symptoms and the excessive anxiety that often provokes these distressing symptoms.

In these cases, Librax as an adjunct can greatly contribute to the course of therapy. Its dual action can offer relief of both painful symptoms and excessive anxiety, because each capsule contains 5 mg chlordiazepoxide HCl and 2.5 mg clidinium Br. The antianxiety action of Librium® (chlordiazepoxide HCl) makes Librax exceptional among drugs for certain gastrointestinal disorders associated with excessive anxiety; the clidinium bromide (Quarzan™) component furnishes dependable antisecretory-antispasmodic action. Dosage is flexible; it may be adjusted according to your patient's requirements within the range of 1 or 2 capsules three or four times daily, up to 8 capsules daily in divided doses.

An adjunct
in anxiety-related upper
functional G.I. disorders

Librax®

Each capsule contains 5 mg chlordiazepoxide HCl and 2.5 mg clidinium Br.

*Rome HP, Brannick TL: Orientation and mechanism of functional disorders: clinicophysiologic correlation, chap. 139, in *Gastroenterology*, edited by Bockus HL. Philadelphia, WB Saunders Company, 1965, p. 1116

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Symptomatic relief of hypersecretion, hyperpotility and anxiety and tension states associated with organic or functional gastrointestinal disorders; and as adjunctive therapy in the management of peptic ulcer, gastritis, duodenitis, irritable bowel syndrome, spastic colitis, and mild ulcerative colitis.

Contraindications: Patients with glaucoma; prostatic hypertrophy and benign bladder neck obstruction; known hypersensitivity to chlordiazepoxide hydrochloride and/or clidinium bromide.

Warnings: Caution patients about possible combined effects with alcohol and other CNS depressants. As with all CNS-acting drugs, caution patients against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving). Though physical and psychological dependence have rarely been reported on recommended doses, use caution in administering Librium (chlordiazepoxide hydrochloride) to known addiction-prone individuals or those who might increase dosage; withdrawal symptoms (including convulsions), following discontinuation of the drug and similar to those seen with barbiturates, have been reported. Use of any drug in pregnancy, lactation, or in women of childbearing age requires that its potential benefits be weighed against its possible hazards. As with all anticholinergic drugs, an inhibiting effect on lactation may occur.

Precautions: In elderly and debilitated, limit dosage to smallest effective amount to preclude development of ataxia, oversedation or confusion (not more than two capsules per day initially; increase gradually as needed and tolerated). Though generally not recommended, if combination therapy with other psychotropics seems indicated, carefully consider individual pharmacologic effects, particularly in use of potentiating drugs such as MAO inhibitors and phenothiazines. Observe usual precautions in presence of impaired renal or hepatic function. Paradoxical reactions (*e.g.*, excitement, stimulation and acute rage) have been reported in psychiatric patients. Employ usual precautions in treatment of anxiety states with evidence of impending depression; suicidal tendencies may be present and protective measures necessary. Variable effects on blood coagulation have been reported very rarely in patients receiving the drug and oral anticoagulants; causal relationship has not been established clinically.

Adverse Reactions: No side effects or manifestations not seen with either compound alone have been reported with Librax. When chlordiazepoxide hydrochloride is used alone, drowsiness, ataxia and confusion may occur, especially in the elderly and debilitated. These are reversible in most instances by proper dosage adjustment, but are also occasionally observed at the lower dosage ranges. In a few instances syncope has been reported. Also encountered are isolated instances of skin eruptions, edema, minor menstrual irregularities, nausea and constipation, extrapyramidal symptoms, increased and decreased libido—all infrequent and generally controlled with dosage reduction; changes in EEG patterns (low-voltage fast activity) may appear during and after treatment; blood dyscrasias (including agranulocytosis), jaundice and hepatic dysfunction have been reported occasionally with chlordiazepoxide hydrochloride, making periodic blood counts and liver function tests advisable during protracted therapy. Adverse effects reported with Librax are typical of anticholinergic agents, *i.e.*, dryness of mouth, blurring of vision, urinary hesitancy and constipation. Constipation has occurred most often when Librax therapy is combined with other spasmolytics and/or low residue diets.

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Med Trib 4

Medical Tribune

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Vol. 17, No. 4 — world news of medicine and its practice—fast, accurate, complete — Wednesday, January 28, 1976

Artificial Skin Tested for Use in Burns

Polymer engineer Prof. Ioannis V. Yannas of MIT holds artificial skin made from carbohydrates and fibers of the protein collagen. Surgeons at Shriners Burns Institute, implanting the material in guinea pigs, find that it is not rejected and that rate of enzymatic degradation can be controlled. Mechanical engineers at MIT designed the material using principles of fiber reinforcement developed in the 1960's for missiles and other space-age hardware.

Psoriasis: Ultraviolet Regimen Less than Year from General Use

By Harriet Page
Special Tribune Correspondent

San Francisco—The PUVA regimen for psoriasis—8-methoxypsoralen plus ultraviolet-A—may be less than a year away from general usage.

Speaking to an SRO audience here at the annual meeting of the American Academy of Dermatology, Drs. Thomas B. Fitzpatrick and John A. Parrish of Harvard Medical School, who pioneered the photochemotherapeutic approach, said FDA approval had been assured in a year or less.

Reached in Washington later, Dr. Carnot Evans, medical officer in charge of the FDA's dermatology section, confirmed this estimate "if no adverse reactions show up." The Boston group is applying for approval of a psoralen manufactured by the Paul B. Elder Co., Inc., of Bryan, Ohio. Dr. Evans noted that Westwood Pharmaceuticals, Inc., of Buffalo, N.Y., has also applied for approval of an oral psoralen.

But whether the FDA will be able to issue guidelines covering the combined photochemotherapeutic approach—that is, guidelines for the oral psoralen dosage plus the safe and effective ultraviolet-A light dosage—remans unclear. Approval for the ultraviolet portion of the treatment would come from a different branch of FDA, the Bureau of Radiological Health.

A number of physicians who spoke here stressed the importance of precise dosimetry in applying UV-A because of the slim margin of safety between the therapeutically effective and toxic doses. Dr. Parrish, for example, told reporters at a press conference that a 20 to 30% overdose of ultraviolet, which could be only 6 or 8 minutes, "can make the difference between ther-

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In Non-Ketotic Diabetes

Resistance to Insulin Held 'Primary Lesion'

Medical Tribune Report

Palo Alto, Calif.—A Stanford University team has put forward new evidence for the view that insulin resistance, rather than insulin deficiency, is the "primary lesion" in non-ketotic diabetes.

Detailing an unusual study of 95 non-obese, non-ketotic subjects, including 21 normal individuals, the team reported that insulin resistance was present in all of the diabetic subjects and suggested that this "accounts for the abnormal glucose intolerance" in such patients.

In a corollary of this view, the investigators advanced the hypothesis that insulin deficiency in some non-ketotic diabetics was a result of pancreatic exhaustion brought about by the "persistently increased insulin secretion" that occurs as a response to the hyperglycemia.

The study was reported by Dr. Ger-

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M.D. Charged with Murder Urges New Euthanasia View

By Michael Herring
Medical Tribune Staff

New York — Because "modern medicine creates 'living corpses' . . . which retain partial biological functions," new, legal definitions of the physician's professional duty, and of human death, are urgently needed to protect doctors against criminal charges.

Dr. Urs Peter Huemmerli, who made these recommendations at a recent conference here sponsored by the Euthanasia Educational Council, based his suggestions on an unusual personal experience. The 49-year-old Swiss internist, chief of medicine at Triemli City Hospital in Zurich, was recently

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FDA Chief Stresses Agency's Law Enforcement Role

Medical Tribune Report

In discussing the FDA's function with Dr. Sackler, Dr. Schmidt emphasized that the agency has no mandate to direct therapeutics in medical practice. *Vicki Lefcourt Photos*

Washington—In an exclusive interview that covered many of the controversial aspects of the work and problems of the Food and Drug Administration, its Commissioner, Dr. Alexander

Text of Interview on Page 13

M. Schmidt, emphasized that it is a law enforcement agency and said of the doctor-patient relationship, "We certainly shouldn't be doing anything to disrupt it."

Questions in the interview were posed by Dr. Arthur M. Sackler, International Publisher of Medical Tribune. The full text of the interview will be published in three installments.

In discussing the function of the FDA in the doctor-patient relationship, Dr. Schmidt pointed out that Dr. Sack-

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Radio-Test Averts Leg Amputation In Ischemic Ulcer

Medical Tribune Report

CHICAGO—A perfusion test using intra-arterial injection of radioactive microspheres may avert premature leg amputation or unnecessarily prolonged hospitalizations in ischemic ulcer, a group from the Johns Hopkins University School of Medicine reports.

A significant relationship was found between the degree of hyperemia and the ability of ischemic ulcer to heal with conservative management, said Dr. Michael E. Siegel of the Division of Nuclear Medicine and Diagnostic Radiology.

On the basis of 60 patients tested, if the degree of relative hyperemia was at least 3.5:1, there was about a 90% possibility that the lesion would heal with conservative management alone.

Criteria Lacking

"Objective criteria for avoiding the unnecessary amputation or expediting the needed amputation are lacking," Dr. Siegel said at the meeting of the Radiological Society of North America. "From our studies, it appears that healing may not be dependent on a palpable pulsatile arterial flow, but more likely is related to the adequacy of the microcirculation and its capacity to produce an inflammatory response with its associated hyperemia, which are inherent in the healing process."

Dr. Siegel suspects that in some patients with arterial diseases, the arterioles may already be maximally dilated secondary to the ischemia, with no further response possible in areas of injury or infection. Thus, the ratio of radioactivity per unit area of the lesion to that of an adjacent area reflects the degree of ischemia at a local or microcirculatory level. This, in turn, may predict whether or not the lesion will heal with conservative measures.

Forty-eight of the 60 patients had no palpable pulses distal to the femoral pulse. Of these, 26 went on to heal with conservative treatment. In 22, amputation was unavoidable.

Twenty-eight patients had diabetes mellitus and were being treated with oral hypoglycemic agents or insulin. Of the 32 without diabetes, 18 went on to heal with conservative management and 14 required amputations.

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Sex Hormones May Benefit Women with Active Arthritis

Medical Tribune Report

MIAMI BEACH, FLA.—Women with active rheumatoid arthritis may respond favorably to intramuscular injections of estrogen and progesterone in quantities similar to the large amounts produced during pregnancy, according to Dr. Harold H. Varon of Baylor College of Medicine, Houston, and John Peter Smith Hospital in Fort Worth, Tex.

Dr. Varon's observations were based on studies of 14 women, ages 39 to 61, all with active seropositive rheumatoid arthritis from six to 23 years' duration. All women in the study were followed for at least six months, and for as long as 23 months after onset of treatment.

Weekly intramuscular injections of estradiol cypionate (1.0 to 2.5 mg), progesterone in oil (100 mg), and medroxyprogestorone acetate (100 mg) were given and responses were often quite dramatic, occurring within a few days, Dr. Varon reported at a meeting of the Southern Medical Association.

Decreased Pain

Patients had a decrease in pain and swelling of the joints, with an increase in strength and range of motion. More dramatic responses were obtained when daily injections of all three hormones were given and when the quantity of medroxyprogesterone acetate was increased to 400 mg. Under these circumstances, Dr. Varon said, swelling and heat in joints were frequently absent upon physical examination within a few days after injections.

Adjunctive therapy was restricted to small doses of aspirin and a diuretic.

Within a few weeks after onset of treatment there was a major subjective and objective reduction in pain, swelling, and inflammation. Progressive increase in strength, decrease in osteoporosis, reduction in elevated sedimentation rates, and correction of anemia were also noted. There have been no recurrences, except when the hormones have been stopped. Side effects have not been severe. Patients occasionally complained of painful episodes when they became ill with acute

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Indications: For the relief of cerebral and peripheral ischemia associated with arterial spasm.
Contraindications: The use of ethaverine hydrochloride is contraindicated in the presence of complete atrioventricular dissociation.
Precautions: Use with caution in patients with glaucoma. Hepatic hypersensitivity has been reported with gastrointestinal symptoms, jaundice, eosinophilia and altered liver function tests. Discontinue drug if these occur.
The safety of ethaverine hydrochloride during pregnancy or lactation has not been established; therefore it should not be used in pregnant women or in women of childbearing age unless, in the judgment of the physician, its use is deemed essential to the welfare of the patient.
Adverse Reactions: Although occurring rarely, the reported side effects of ethaverine include nausea, abdominal distress, hypotension, anorexia, constipation or diarrhea, skin rash, malaise, drowsiness, vertigo, sweating, and headache.
Dosage and Administration: One capsule three times a day.
How Supplied: 100 mg capsules in bottles of 50 and 500.

Replacement Estrogen Pros & Cons Weighed

By ALAN FITZGIBBON
Special Tribune Correspondent

ROCKVILLE, MD.—The Food and Drug Administration is considering—and is likely to put into effect—a recommendation from its Obstetric and Gynecology Advisory Committee that physicians and patients be warned about potential risks of using replacement estrogens to treat menopausal and postmenopausal complaints.

The committee made its recommendation three days after a meeting here in which it heard seven reports which tended to associate the increased use of conjugated estrogens with increased endometrial carcinoma and six reports by investigators who found more benefits than risks in the use of the drugs.

Though serious questions were raised about estrogens' carcinogenic potential, several speakers—including those who doubted the agents' safety—emphasized that no direct link had been established between estrogen use and endometrial cancer.

Concern Aroused

Two studies of the drugs' possible carcinogenicity described in the December 4 issue of the *New England Journal of Medicine* aroused concern about their use, and the committee promptly decided to put estrogens on its agenda.

Representatives of the research teams that conducted the *N. Eng. J. Med.* published studies described them in somewhat greater detail. William Finkel, Ph.D., of the Kaiser Permanente Medical Center, Los Angeles, and Dr. Donald Smith, of the University of Washington School of Medicine, Seattle, said their respective groups retrospectively determined the estrogen use patterns of women who developed endometrial carcinoma and matched patients with other cancers or without cancer. Among the 282 women in the Los Angeles group, 57% of the endometrial carcinoma patients had used estrogens but only 15% of the controls had done so. Among the 634 patients in Seattle, 152 of the 317 women with endometrial cancer had used estrogens but only 54 in the like-sized control group had used estrogens.

On the basis of the Los Angeles and Seattle data, it was calculated that estrogen users ran a 4.5 to 7.6 greater risk of developing carcinoma of the uterine endometrium than nonusers.

Dr. Thomas Mack, director of cancer surveillance at the University of Southern California School of Medicine, Los Angeles, described a third study at the meeting.

Other Risks Eliminated

Its locale was a large retirement community in Southern California and its investigative population was 65 women who developed endometrial carcinoma during the past four years. Each of the patients was matched with four women who did not develop the cancer. All survivors were interviewed, other known risk factors such as obesity were eliminated, and pharmacy records were checked to exclude other possibly carcinogenic drugs from consideration.

Dr. Mack said that among conclusions from the study were that the risk of developing endometrial carcinoma was greater among postmenopausal estrogen users than their combined risk of developing cancers of the breast, lungs, ovary, and colon, and that the more estrogen they took the greater their risk of endometrial cancer.

Dr. Donald Austin, director of the tumor registry in the California Department of Health, Berkeley, who had previously reported a 50% increase in endometrial carcinoma between 1969 and 1973 in five counties surrounding San Francisco Bay, told the committee that the increase was confined to women over 50 years of age and had occurred mostly among upper middle-class women who were consequently more prone to take prescription medications to relieve discomforts.

Dr. Sidney M. Wolfe, director of the consumer-oriented Health Research Group in Washington, noted in an unscheduled presentation that 7.5 million estrogen prescriptions were written in the year ended June 30, 1975. He estimated that 60% of users take their prescribed drug for more than three months and that the median length of use is about 10 years.

He added that 2.1 million women take estrogens largely to counter the effects of aging, and attacked this and other uses not related to menopausal complaints as dangerous and unwarranted.

Benefits Cited

Reiterating the point that no direct link has yet been established between estrogen use and endometrial cancer, and emphasizing the benefits of replacement therapy for many women, other speakers urged that caution be observed in considering any possible restrictions on the drug's use at this time.

"With lengthening of life, normal women now live more than a third of their lives with dramatically reduced estrogen levels, regardless of the source," said Dr. Charles B. Hammond, Associate Professor of Obstetrics and Gynecology at Duke University Medical Center. He noted that about one-quarter of women consult their physicians about symptoms relating to menopause.

"Approximately 10 to 15% of women will have menopausal symptoms that are obviously caused by reduced estrogen levels and would be very successfully treated by estrogen replacement therapy," he added.

Dr. Daniel W. Cramer, an obstetrics-gynecology resident at Boston Hospital for Women-Harvard Medical School who spent two years as a research epidemiologist at the National Cancer Institute, said that a "study of the trends of endometrial cancer over the period 1947-70 did not show any significant change in the morbidity and mortality of this disease."

He noted several factors that might obscure the real situation, including varying diagnostic criteria, hysterectomy, and inaccuracy in recording the site of cancer origin, and concluded that his work "cannot be considered a refutation of studies linking endometrial carcinoma and exogenous estrogen, but neither does it lend any support to the hypothesis."

Bernard G. Greenberg, Ph.D., Dean of and Kenan Professor of Biostatistics at the University of North Carolina School of Public Health, commented:

More Studies Needed

"It would be premature to impose any ban or restriction on use of estrogen therapy at this time. Obviously, the millions of women using this drug derive considerable medical benefit from it in the way of controlling weight, decreasing the thinning out of bone tissue, slowing down the processes of aging, perhaps prevention of heart attacks, and a general feeling of well-being. . . .

"What is needed now are more epidemiological studies designed more validly than the Los Angeles and Seattle one using other groups of cases and comparison individuals. I would especially like to see a comparison group of women with breast cancers. Furthermore, one must examine the question of dosage schedule, duration of therapy, and the conjoint use of progestins.

"It may very well be that the use of estrogens should be recommended in conjunction with the periodic use of a progestin added to counteract any proliferation of the endometrium. Similarly, we should learn more about restrictions on duration of therapy, dosage, age of patient when the dosage may be most dangerous, and other factors in the patient that may be contraindications for such therapy."

To Pituitary Via Nose

Dr. Keat Jin Lee, with self-retaining retractor, a new surgical instrument for simplifying removal of the pituitary via the nose. It was invented by Dr. Lee and colleagues at the Hospital of St. Raphael, New Haven.

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CLINICAL NEWS NOTE: *"Objective criteria for avoiding the unnecessary amputation or expediting the needed [leg] amputation [in ischemic ulcer] are lacking. From our studies, it appears that healing may not be dependent on a palpable pulsatile arterial flow, but more likely is related to the adequacy of the microcirculation and its capacity to provide an inflammatory response with its associated hyperemia, which are inherent in the healing process."* (Dr. Michael E. Siegel, Johns Hopkins University School of Medicine. See page 2.)

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Circulation audited by Business Publications Audit of Circulation, Inc.

MEDICAL TRIBUNE *is published each Wednesday except on March 31, June 2, June 16, June 30, July 14, July 28, Aug. 11, Aug. 25, Sept. 29, Dec. 1, Dec. 22, Dec. 29, by Medical Tribune, Inc., 880 Third Ave., New York, N.Y., 10022 Controlled circulation postage paid at Vineland, N.J. 08360 Subscriptions $25.00, Students $7.50.*

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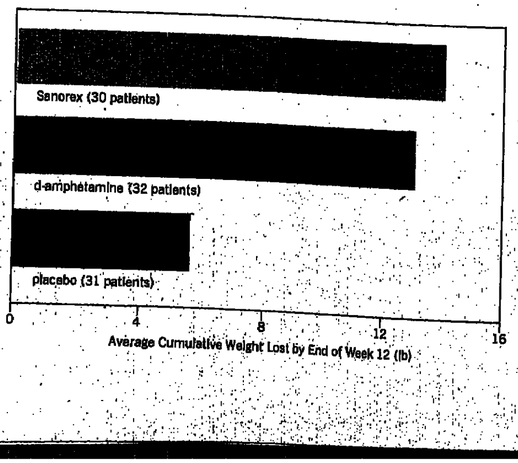

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*The significance of these differences for humans is uncertain.

For Brief Summary, please see facing page.

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1. Vernace BJ: Practical considerations for managing obese patients: Initial interview and efficacy treatment in the office. Scientific Exhibit presented at the American Medical Association, 27th Clinical Convention, Anaheim, Calif., Dec 1-4, 1973.

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Contraindications: Glaucoma; hypersensitivity or idiosyncrasy to the drug; agitated states; history of drug abuse; during, or within 14 days following, administration of monoamine oxidase inhibitors (hypertensive crisis may result).
Warnings: Tolerance to many anorectic drugs may develop within a few weeks; if this occurs, do not exceed recommended dose, but discontinue drug. May impair ability to engage in potentially hazardous activities, such as operating machinery or driving a motor vehicle, and patient should be cautioned accordingly.
Drug Interactions: May decrease the hypotensive effect of guanethidine; patients should be monitored accordingly. May markedly potentiate pressor effect of exogenous catecholamines; if a patient recently taking mazindol must be given pressor amine agents (e.g., levarterenol or isoproterenol) for shock (e.g., from a myocardial infarction), extreme care should be taken in monitoring blood pressure at frequent intervals and initiating pressor therapy with a low initial dose and careful titration.
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Adverse Reactions: Most commonly, dry mouth, tachycardia, constipation, nervousness, and insomnia. *Cardiovascular:* Palpitation, tachycardia. *Central Nervous System:* Overstimulation, restlessness, dizziness, insomnia, dysphoria, tremor, headache, depression, drowsiness, weakness. *Gastrointestinal:* Dryness of mouth, unpleasant taste, diarrhea, constipation, nausea, other gastrointestinal disturbances. *Skin:* Rash, excessive sweating, clammminess. *Endocrine:* Impotence, changes in libido have rarely been observed. *Eye:* Long-term treatment with high doses in dogs resulted in some corneal opacities, reversible on cessation of medication; no such effect has been observed in humans.
Dosage and Administration: 1 mg three times daily, one hour before meals, or 2 mg per day, taken one hour before lunch in a single dose.
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Single Brain Amine Theory In Mental Illnesses Unproved

Medical Tribune Report

SANTA MONICA, CALIF.—Old theories about the biochemical basis of mental illness do not appear to be strengthened by recent clinical findings reported by Dr. Frederick Goodwin, Chief of the Psychiatry Section of the National Institute of Mental Health's Intramural Research Program. The findings were based on an analysis of metabolites of brain amines in the spinal fluid of patients afflicted with mania, depression and schizophrenia.

The NIMH study concluded that it is still not possible to link any single brain amine with specific illness, even though many theories abound suggesting that an increase or decrease in certain brain amines may be reflected concomitantly in a manic "high" or a depressed psychic "low," Dr. Goodwin told the 1975 Symposium of the Intra-Science Research Foundation.

Although levels of 5-HIAA (5-hydroxy indole acetic acid) were lower in the spinal fluid of depressed patients than they were in the spinal fluid of normals, it was not present in excessive amounts in the CSF of manic patients, as some theories proposed. In fact, he said, the CSF of some manics contained subnormal amounts of HIAA.

Similarly, Dr. Goodwin could find no strong correlation between spinal fluid levels of the dopamine metabolite homovanillic acid (HVA) and the norepinephrine metabolic 3-methoxy-4-hydroxyphenyl glycol (MHPG) in the CSF of manic patients.

An association between schizophrenia and brain amine metabolites in the CSF is equally unconvincing, Dr. Goodwin told the symposium. Although some theories propose that schizophrenic patients metabolize dopamine to HVA more rapidly than normal individuals do, the NIMH researchers, along with Dr. Malcolm Bowers of Yale, found that during or after a schizophrenic interlude, the turnover rate of dopamine may decline.

Not Convincing

As for establishing a link between drugs now used to treat various mental disorders, and brain amine theories of the past, Dr. Goodwin said that the NIMH findings are again not convincing. Depressed patients treated with lithium salts, tricyclic drugs or electroconvulsive shock usually showed a reduction in the spinal fluid metabolites, rather than the expected increase. Also, phenothiazine drugs used to treat schizophrenia were associated with an increase of HVA in patients treated for a short time but no increase when the patients were treated with the drug for periods of from three to 10 weeks.

In the past, said Dr. Goodwin, making a firm connection between specific brain amines and a specific psychic disorder was thwarted by the obvious difficulties of analyzing those substances in the brains of living individuals. In addition, analysis of the same materials in the brains of suicides who were presumably psychotic gave very inconsistent results. The alternative was to measure the metabolites which enter the spinal cord from the brain by way of the cerebral ventricles.

Dr. Goodwin's findings were supported in general in a paper presented by Dr. William E. Bunney, Jr., Chief of the Adult Psychiatry Branch at NIMH. Based on extensive studies of drug effects, measurements of metabolites in the urine and CSF, etc., he observed that although drugs which influence the levls of norepinephrine appear to decrease or activate mania or depression, they also affect other brain amines, such as serotonin. Drugs which present theories indicate should reduce depression or mania "produce only minimal behavioral change."

Concluding that "the CSF metabolite data do not support a single amine model," Dr. Goodwin proposed that the mixed results may mean that a disturbance in one amine system sets off an imbalance in one or more other systems. Alternatively, he said, there may be subgroups within different disease states, each of which might have a characteristic brain amine abnormality.

Insulin Resistance in Non-Ketotic Diabetes

Continued from page 1

nld M. Reaven, who said it was undertaken with Drs. Robert Bernstein and Jerrold M. Olefsky, in an effort to throw more light on the relationship between insulin resistance and insulin deficiency in non-ketotic diabetes.

In presenting the findings, the team pointed out that a variety of studies, most notably those of Berson and Yallow, have shown that patients with non-ketotic diabetes are "insensitive to the biologic action of insulin" and that these patients have circulating levels of plasma immunoreactive insulin "at least as high as those seen in normal subjects." What has been missing, the research group stressed, is information that defines the role of insulin resistance and insulin deficiency in the diabetic syndrome.

"Most studies have focused on either the plasma insulin response to glucose or the ability of exogenous insulin to lower glucose, and have not attempted to study both aspects of the problem in the same populaton," the report declared.

This was the aim of the Stanford study.

The 95 subjects in the investigation, none of whom had ever received insulin, were divided into five groups on the basis of their plasma glucose response to an oral glucose tolerance test. The groups included 21 normal subjects, 27 with borderline tolerance, 27 with chemical diabetes, nine with fasting hyperglycemia (110-150 mg%) and 11 with fasting hyperglycemia above 150 mg %.

Following an overnight fast, all subjects received a 150-minute continuous infusion of glucose, insulin, epinephrine and propranolol. Under these conditions, the team explained, endogenous insulin secretion was suppressed and similar insulin levels were achieved in all subjects, thus making it possible to compare the ability of different subjects to dispose of identical glucose loads under the same insulin stimulus.

Disparate Patterns

"The mean plasma insulin response of patients with either borderline abnormalities of glucose tolerance or chemical diabetes was equal to or greater than that of normal subjects at all points during the glucose tolerance test," the investigators said. "Thus, the glucose intolerance of two patient groups cannot be attributed to insulin lack.

"On the other hand," the team continued, "the mean insulin response of patients with moderate fasting hyperglycemia was somewhat attenuated, and patients with severe fasting hyperglycemia had unequivocal insulin deficiency."

Overall, however, all four patient groups with abnormal carbohydrate metabolism displayed more resistance than normal subjects to the action of insulin.

In discussing the findings, the team observed that the disparate patterns of insulin response in the patients with borderline glucose tolerance and chemical diabetes and in those with hyperglycemia could be explained by two hypotheses. The first proposes that the basic lesion in diabetes is insulin deficiency, from which it "logically follows," the investigators said, that the diagnosis of diabetes would be reserved for subjects with significant fasting hyperglycemia, since these were the only ones who demonstrate an abnormally low insulin response to the glucose challenge. Patients with a lesser degree of glucose intolerance, who are not insulin deficient, would be classified simply as "the tail of the bell-shaped curve of the normal population."

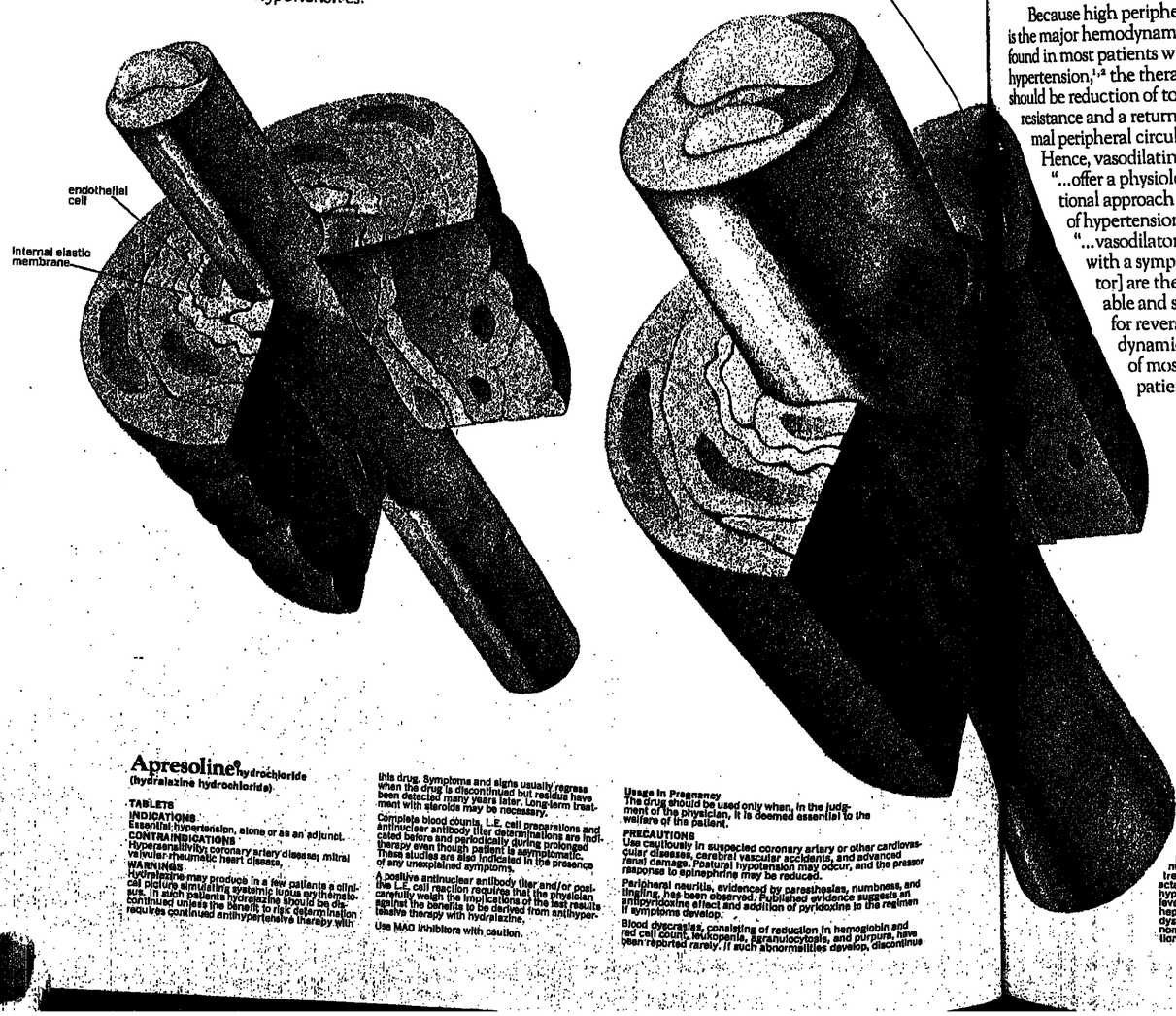
"The second interpretation of our results," the group suggested," begins by viewing diabetes mellitus as a disease made up of a continuous spectrum of individuals with varying degrees of glucose intolerance, with the severity of the hyperglycemia dependent upon each patient's degree of insulin resistance and/or deficiency. In this case, the primary lesion in diabetes is resistance to the action of insulin, and the physiologic response is to increase insulin secretion in an attempt to minimize hyperglycemia. However, the continuous need to maintain an increased secretion of insulin could lead to pancreatic exhaustion with the subsequent development of insulin deficiency. In this formulation, insulin resistance is the basic defect in non-ketotic diabetes, and insulin deficiency is viewed as a secondary phenomenon."

That formulation, the team said, reflects its "current views." "Implicit is the belief that individuals classified as having non-ketotic diabetes by today's criteria do not comprise a homogeneous population, and that at least two distinct disease processes are present in such patients. . . . [This] conclusion is offered as a hypothesis which is consistent with available information and subject to evaluation by further trials."

Apresoline® (hydralazine) relaxes arterioles to solve the major hemodynamic problem in hypertension

Abnormally high peripheral resistance is the major hemodynamic problem with most hypertensives.

Apresoline reduces peripheral resistance and lowers blood pressure through a direct relaxation of arteriolar smooth muscle.



high peripheral resistance: common attribute of most hypertensives

Because high peripheral resistance is the major hemodynamic disturbance found in most patients with essential hypertension,[1,2] the therapeutic goal should be reduction of total peripheral resistance and a return to more normal peripheral circulation.[1,2]

Hence, vasodilating drugs "...offer a physiologically rational approach to the therapy of hypertension."[1] In addition, "...vasodilators [combined with a sympathetic inhibitor] are the most predictable and specific drugs for reversing the hemodynamic abnormality of most hypertensive patients."[1]

the only oral agent that deals directly with this problem

Apresoline (hydralazine), the only currently approved oral antihypertensive with vasodilating action, decreases peripheral resistance—regardless of its cause—and, hence, arterial pressure by relaxing arteriolar smooth muscle. Accompanying the fall in blood pressure is a rise in cardiac output and rate. Apresoline also maintains or increases renal and cerebral blood flow.

a different and complementary pharmacologic approach

Different in action from all other oral antihypertensives and compatible with most of them, Apresoline can play a significant role in a variety of therapeutic combinations.

Such combinations, according to Freis,[3] with each component representing a different antihypertensive mechanism, provide the most effective way to control blood pressure. This approach may also permit lower drug dosages.

the problem of postural hypotension minimized

Nickerson[4] describes the action of Apresoline as follows:

"A preferential effect on arterioles, as compared to veins, allows the increase in cardiac output and minimizes postural hypotension; the latter is much less than that produced by agents blocking sympathetic nerves."

Continued on following page

Apresoline® hydrochloride
(hydralazine hydrochloride).

TABLETS

INDICATIONS
Essential hypertension, alone or as an adjunct.

CONTRAINDICATIONS
Hypersensitivity; coronary artery disease; mitral valvular rheumatic heart disease.

WARNINGS
Hydralazine may produce in a few patients a clinical picture simulating systemic lupus erythematosus. In such patients hydralazine should be discontinued unless the benefits to risk determination requires continued antihypertensive therapy with this drug. Symptoms and signs usually regress when the drug is discontinued but residua have been detected many years later. Long-term treatment with steroids may be necessary.

Complete blood counts, L.E. cell preparations and antinuclear antibody titer determinations are indicated before and periodically during prolonged therapy even though patient is asymptomatic. These studies are also indicated in the presence of any unexplained symptoms.

A positive antinuclear antibody titer and/or positive L.E. cell reaction requires that the physician carefully weigh the implications of the test results against the benefits to be derived from antihypertensive therapy with hydralazine.

Use MAO inhibitors with caution.

Usage in Pregnancy
The drug should be used only when, in the judgment of the physician, it is deemed essential to the welfare of the patient.

PRECAUTIONS
Use cautiously in suspected coronary artery or other cardiovascular diseases, cerebral vascular accidents, and advanced renal damage. Postural hypotension may occur, and the pressor response to epinephrine may be reduced.

Peripheral neuritis, evidenced by paresthesias, numbness, and tingling, has been observed. Published evidence suggests an antipyridoxine effect and addition of pyridoxine to the regimen if symptoms develop.

Blood dyscrasias, consisting of reduction in hemoglobin and red cell count, leukopenia, agranulocytosis, and purpura, have been reported rarely. If such abnormalities develop, discontinue therapy. Periodic blood counts are advised during prolonged therapy.

ADVERSE REACTIONS
Common: Headache; palpitations; anorexia; nausea; vomiting; diarrhea; tachycardia; angina pectoris. *Less frequent:* Nasal congestion; flushing; lacrimation; conjunctivitis; peripheral neuritis, evidenced by paresthesias, numbness, and tingling; edema; dizziness; tremors; muscle cramps; psychotic reactions characterized by depression, disorientation, or anxiety; hypersensitivity (including rash, urticaria, pruritus, fever, chills, arthralgia, eosinophilia, and, rarely, hepatitis); constipation; difficulty in micturition; dyspnea; paralytic ileus; lymphadenopathy; splenomegaly; blood dyscrasias, consisting of reduction in hemoglobin and red cell count, leukopenia, agranulocytosis, and purpura; hypotension; paradoxical pressor response.

DOSAGE
Initiate therapy in gradually increasing dosages; adjust according to individual response. Start with 10 mg 4 times daily for the first 2 to 4 days, increase to 25 mg 4 times daily for balance of first week. For second and subsequent weeks, increase dosage to 50 mg 4 times daily. For maintenance, adjust dosage to lowest effective level.

The incidence of toxic reactions, particularly the L.E. cell syndrome, is high in the group of patients receiving large doses of Apresoline.

In a few resistant patients, up to 300 mg Apresoline daily may be required for a significant antihypertensive effect. In such cases, a lower dosage of Apresoline combined with a thiazide, reserpine, or both may be considered. However, when combining therapy, individual titration is essential to insure the lowest possible therapeutic dose of each drug.

HOW SUPPLIED
Tablets, 10 mg (pale yellow, dry-coated); bottles of 30, 60, 100 and 1000.

Tablets, 25 mg (deep blue, dry-coated) and 50 mg (lilac, dry-coated); bottles of 30, 60, 100, 500 and 1000.

Tablets, 100 mg (peach, dry-coated); bottles of 100.

Consult complete literature before prescribing.

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حكمت الكحول

Apresoline®
(hydralazine)
...key component in the "guideline" antihypertensive regimens

AMA Committee on Hypertension Recommendations

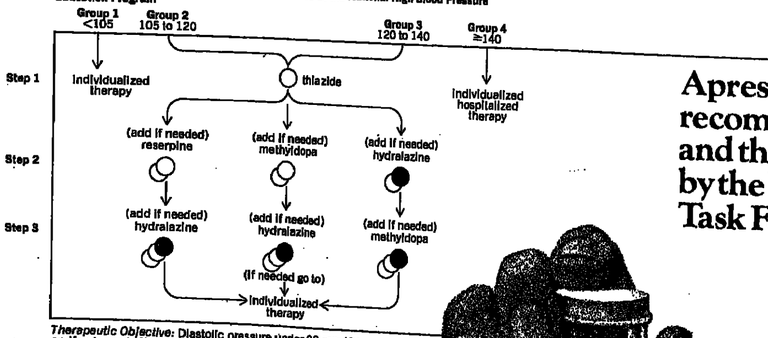
Table 1.—Regimens for the Management of Uncomplicated Hypertension

	Alternative 1	Alternative 2	Alternative 3*	Alternative 4
Initial therapy	Thiazide diuretic	Thiazide diuretic	Thiazide and guanethidine	Thiazide diuretic
Add, if necessary	Methyldopa	Reserpine	Methyldopa and hydralazine or both	Propranolol (unlabeled use)
	Hydralazine	Hydralazine		Hydralazine

*In patients who cannot tolerate guanethidine, alternatives 1 or 4 may be given a therapeutic trial, but treatment should be initiated with *both* the diuretic and methyldopa or propranolol.

(Adapted[6])

Recommendations by the Hypertension Task Force of the National High Blood Pressure Education Program



Therapeutic Objective: Diastolic pressure under 90 mm Hg, or, if untoward effects cannot be tolerated, under 100 mm Hg.

(Adapted[7])

Apresoline... included in all four treatment plans by the AMA Committee[6]

Apresoline... recommended second and third step therapy by the Hypertension Task Force[7]

used effectively in the landmark VA studies[8,9]

Apresoline was one of the three basic drugs used in two published VA cooperative studies—studies which demonstrated conclusively the benefits of antihypertensive treatment in reducing risk of morbidity and mortality.

Apresoline®... (hydralazine) An antihypertensive idea whose time has come

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EDITORIAL CAPSULES

. . . brief summaries of editorials or comments in current medical and scientific journals.

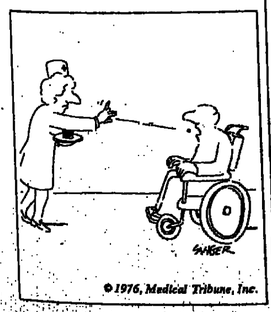
"Our Lives and Hard Times"

". . . Medicine never has been, and never will be, solely a matter of prevention; nor is high technology the only means to therapeutic or preventive progress . . . We do already spend quite a lot on prevention of various sorts. Even so, the opportunity and many of the means for a better preventive capacity than we now have in the field of chronic disease are at hand and the need is more pressing than ever. Increasing effectiveness and efficiency in cure and care might provide some of the wherewithal, but the X% mentality [a combination of cumbersome planning, innate cautiousness and sense of fair play that fails to make a radical shift in the use of health resources in order to prevent chronic disease] is what we really have to overcome.

"There is, however, another difficulty. Sick patients have names; they present immediate problems, which appeal to those we choose and train as doctors. Those whose illnesses we may forestall are usually, almost by definition, nameless, faceless, and unidentifiable either to themselves or to others. There is a challenge here to medical education, as well as practice and research.

"Hard times have provided us with the chance and the incentive to make what could be some of the most significant advances in health of modern times. If we were at war, we should act as though our lives depended on what we did—which of course they do—and we should almost certainly succeed; but we can't quite talk ourselves into this frame of mind, and it is difficult to be optimistic about the outcome.

"We shall, presumably, muddle through, and enjoy better times—but the X% mentality and medicine's predominant concern with the sick rather than the healthy will prevail, then as now. My guess is that in 20 or 30 years, or whenever it is that we have to tighten our belts again, we shall look back at the opportunities we had in the 1970s, hard though the times were, and have to confess that we let them slip by, unexploited." (*Caradog Jones Lecture, T. W. Meade, M.R.C., D.H.S.S., Lancet 2:1053, Nov. 29, 1975*)



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Study Shows Hypertension No Longer a 'Silent Epidemic'

Medical Tribune Report

BETHESDA, MD.—Hypertension no longer deserves the designation of a "silent epidemic," according to data suggesting that both patients and physicians have become more aware of the disorder and its dangers since the advent of the National High Blood Pressure Education Program in 1972.

The data—based on the National Disease and Therapeutic Index—show that the number of patients making their first visit to a doctor for the specific purpose of getting a blood pressure reading has increased 38% since the government-sponsored program began and that total patient visits for hypertension or hypertensive heart disease have jumped more than 40% in the same period of time.

6 Million Unaware

This, Dr. Robert Levy told a news conference at the National Heart and Lung Institute, indicates greater awareness of hypertension as a reason for seeing a doctor than all other causes combined.

Dr. Levy, Director of the NHLI, also reported the results of a 14-community study—thought to be representative of the nation as a whole—made in 1973-74. If indeed the survey is representative, he said, only 29% of the 23 million adult Americans thought to have hypertension are now unaware of it, compared with the 49% found by surveys in the early 1960s and in 1971.

Dr. Levy was quick to point out, however, that an estimated 6 million citizens still are hypertensive without knowing it and that the problem appears to be more prevalent among males than among females, particularly in the black community. By contrast, he said, 80% of women, regardless of race, apparently have their blood pressure regularly checked.

Turning from detection to therapy, Dr. Levy reported that the number of patients receiving sufficient treatment to keep their blood pressure within normal limits has almost doubled since 1971. But, he said, more than 9 million of the nation's estimated 23 million adult hypertensives—while aware of having the disorder—are receiving either no treatment whatsoever or not enough.

In these categories, he said, are both those who choose to ignore the problem because the risks of renal, cardiovascular or cerebrovascular complications seem remote and those who discontinue their medication once they begin to feel better in the mistaken belief that the danger has passed. Still others—having experienced side effects from the drugs—want no further part of a regimen that makes them feel worse than they did before, he explained.

In this connection, Dr. Levy and members of the High Blood Pressure Coordinating Group who were present endorsed the concept of "therapeutic alliances between patients and their physicians to help patients help themselves." Of particular importance, they said, are:

- adequate explanations for dietary instructions such as the need to restrict salt intake and lose weight;
- prompt attention to side-effects such as gout whose expression is often prompted by thiazide diuretics;
- a willingness to try substituting other drugs in the hypertension armamentarium when those first prescribed —for whatever reason—prove less than ideal;
- ongoing efforts to impress on patients that hypertension is a chronic disorder requiring life-long therapy and that, for each 10 points of increase of diastolic pressure over normal limits there is a concomitant increase of risk.
- equal emphasis on the fact that adequate control of hypertension can add as much as 18 years to life expectancy.

More than 150 lay and professional organizations—such as the American Medical Association, the National Medical Association, the American Hospital Association, the American Osteopathic Association, the American College of Cardiology and the American Heart Association—participate in this outreach and educational program which is coordinated by the NHLI.

The program's future plans include educational efforts directed at high school students and a detailed cost-benefit analysis of hypertension control to refine the planning process in the years ahead.

Psoriasis Therapy: Ultraviolet + Psoralen

Continued from page 1

apy and a severe, blistering burn, especially with non-tanning subjects." And Dr. Eugene M. Farber, of Stanford University, said patient demand for PUVA therapy has resulted in the use of "jerry-built" lamps that lack uniform intensity, have no safety devices, and require an inordinate time exposure.

The Boston group has been working with th GTE Sylvania Co., which is partially funding a 16-center cooperative study now underway. Dr. Fitzpatrick expressed full approval of the lights developed by Sylvania, but Dr. Parrish noted that industry is "poised and ready" to deliver lighting systems as soon as the therapy receives FDA approval.

Their approach, Dr. Parrish said, is to keep two factors in the three-factor therapy constant. Thus, the dose of psoralen is calculated on a mg/kg table, and time from drug ingestion to light therapy is kept constant at two to three hours. Light exposure is calculated in joules, or milliwatts per unit area multiplied by time.

Dr. Klaus Wolff, of the University of Vienna, who has been collaborating with the Harvard group for a number of years, said minimum phototoxic dose is determined for each patient by exposing small patches of unexposed skin —such as the buttocks—to different light doses of .5, 1, and 3 joules. Seventy-two hours later, the test fields are graded for photosensitivity. The minimum phototoxic dose is that which produces a test field of "barely perceptible redness," he said.

Another problem with lighting systems, Dr. Fitzpatrick said, is that lamps may lose their effectiveness after only several hundred hours.

Light Output Varies

A paper by Drs. John S. Martin and Henry H. Roenigk, of the Cleveland Clinic, described a study of 168 patients using Sylvania and GE lighting systems of varying output. While the stronger Sylvania system required less time to clear up psoriatic lesions, the risk of burns was greater. And, they found, while the Sylvania unit had an initial output of 17 milliwatts/cm², this reading had dropped to 8 milliwatts/cm² after three months of use and all the bulbs needed changing. The General Electric systems they use have had a fall-off of about 5% in eight months and have not needed replacement. "Measurements of output with a photometer are necessary," they concluded, "and close supervision by trained technicians will avoid complications."

As to the overall safety of the PUVA approach, Drs. Parrish and Fitzpatrick said careful monitoring of a number of parameters has not yet revealed toxic side effects except burning when light doses are too heavy. "We haven't seen any abnormalities in liver, kidney, or blood," Dr. Parrish said. "Both skin cancer and cataracts were demonstrated in rats using 1,000 times the drug dose and more than 10 times the light exposure. But controlled laboratory and clinical studies must continue."

Dermatologists have had some 25 years experience with the psoralens in the treatment of vitiligo, Dr. Parrish continued, and have found no toxicity. "But we know that sunlight can cause skin cancer, and we know it can produce early aging of the skin, so we must continue to be alert for those two effects, especially in the younger patient requiring long-term maintenance treatment."

Meanwhile, he said, a number of safety precautions are being observed. PUVA is given every other day, because of the photosensitivity reaction to psoralen may peak as late as 72 hours after oral administration of the agent. Patients wear protective glasses during treatment, but are also asked to wear sunglasses and sunscreens throughout the day and to avoid sun exposure that day.

Meanwhile, the collaborative study has already entered 640 patients and plans to treat a total of 1,600, using a standard protocol. The Boston and Vienna centers have so far treated 300 patients, and a 20-center study is being started in Europe, according to Dr. Wolff.

But, cautioned Dr. Farber, "since sequelae from PUVA treatment may not surface immediately, it is essential for practitioners to wait until the cooperative clinical trials are completed."

no place to hide

Today's woman can't hide an unsightly dermatosis, making effective treatment a necessity.

With its unique four-way action, Vioform®-Hydrocortisone provides the kind of comprehensive therapy that many common dermatoses* require, particularly those infected with fungi or bacteria.

*This drug has been evaluated as possibly ineffective for these indications. See brief prescribing information.

Vioform®-Hydrocortisone
(iodochlorhydroxyquin and hydrocortisone)

INDICATIONS
Based on a review of this drug by the National Academy of Sciences-National Research Council and/or other information, FDA has classified the indications as follows: possibly effective: Contact or atopic dermatitis; lichenified/eczematous mammular eczema; infantile eczema; endogenous eczema; chronic infectious dermatitis; stasis dermatitis; pyoderma; nuchal eczema and chronic eczematoid otitis externa; acne urticata; localized or disseminated neurodermatitis; lichen simplex chronicus; pruritus (vulvae, scroti, ani); folliculitis; bacterial dermatoses; mycotic dermatoses such as tinea capitis, cruris, corporis, pedis); monilasis; intertrigo.
Final classification of the less-than-effective indications requires further investigation.

CONTRAINDICATIONS
Hypersensitivity to Vioform-Hydrocortisone, or any of its ingredients or related compounds; lesions of the eye; tuberculosis of the skin; most viral skin lesions (including herpes simplex, vaccinia, and varicella).

WARNINGS
This product is not for ophthalmic use.
In the presence of systemic infections, appropriate systemic antibiotics should be used.

Usage in Pregnancy
Although topical steroids have not been reported to have an adverse effect on pregnancy, the safety of their use in pregnant females has not been established. Therefore, they should not be used extensively on pregnant patients in large amounts or for prolonged periods of time.

PRECAUTIONS
May prove irritating to sensitized skin in rare cases. If this occurs, discontinue therapy. May stain.

If used under occlusive dressings or for a prolonged period, watch for signs of pituitary-adrenal axis suppression.

May interfere with thyroid function tests. Wait at least one month after discontinuance of therapy before performing these tests. The ferric chloride test for phenylketonuria (PKU) can yield a false-positive result if Vioform is present in the diaper or urine.

Prolonged use may result in overgrowth of non-susceptible organisms requiring appropriate therapy.

ADVERSE REACTIONS
Few reports include: hypersensitivity, local burning, irritation, pruritus. Discontinue if untoward reaction occurs. Rarely, topical corticosteroids may cause striae at site of application when used for long periods in inguinal areas.

DOSAGE
Apply a thin layer to affected areas 3 or 4 times daily.

HOW SUPPLIED
Cream, 3% iodochlorhydroxyquin and 1% hydrocortisone in a water-washable base containing stearyl alcohol, cetyl alcohol, stearic acid, petrolatum, sodium lauryl sulfate, and glycerin in water; tubes of ½ and 1 ounce. *Mild Ointment*, 3% iodochlorhydroxyquin and 0.5% hydrocortisone in a petrolatum base; tubes of 1 ounce.

Consult complete product literature before prescribing.

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the most widely prescribed form... 20 Gm. Cream

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On 'Extasin and Miserin'

Reflections after reading an address by a new Honorary Fellow and Special Visitor of the Imperial College of Science and Technology, London.

LORD ROTHSCHILD, for many years director general of the United Kingdom's Central Policy Review Staff or "think tank," has postulated the future creation of two new pills containing chemical substances that he calls "Extasin" and "Miserin." He had observed that rats with implanted cerebral electrodes "can be taught to switch the electricity on when they feel like it, and it turns out that the pleasure is so intense that when the rats are presented with their equivalent of caviar or Marilyn Monroe, they ignore these stimuli and continue to press the pleasure button."

As is so often the case with the most prescient of government officials, past history appears to outstrip their "wildest" imaginings for the future. One would expect that from an island kingdom where scotch and gin found their origins, the realization would have penetrated that for centuries many a man actually has foregone the equivalent of caviar and Marilyn Monroe for the "ecstasies" of the bottle. To replace a liquid with a pill is no great scientific breakthrough. *Further, we can assure* Lord Rothschild that any substance such as his new "Extasin" would probably be prohibited by the British Medicine's Commission and our FDA if it had one one-hundredth of the addicting and toxic potential of our old "Extasins"—alcohol, morphine and tobacco. In fact, in our country they would be limited to animal studies and probably prohibited in clinical pharmacologic studies. There is, therefore, little likelihood of a better or safer "pleasure pill" or new "ecstasy chemical," thanks to the Drug Policy Review staffs of most governments.

As to "Miserin," or Lord Rothschild's "intense misery pills," here *again our performance has outstripped* his projection. Apomorphine, an old drug, can fill that bill. A possible "drawback" is its parenteral use.

In discussing the biologic potentials that man now possesses, including cloning, Lord Rothschild goes on to say that with such and other technical procedures of human intervention, "evolution will be bypassed or short-circuited. Cutting out millions of years of trial and error really makes one think." On *the basis of the record, DID IT?*

A.M.S.

Dangers Ahead

THE YEAR 1976 IS NOTEWORTHY as a bicentennial year but it is also one in which a presidential election will be held. To what degree the one event will overshadow the other remains to be seen but it would be salutary if politicians and legislators would reflect on the origins of this republic.

It is clear that the founders of our sovereign state were extraordinarily concerned to set limits upon the powers of the federal government, which is not intrinsically surprising, since the U.S.A. came into being by rebellion against the excesses of those previously governing this country. But all governments—bar none—seek to increase their domain of operative control and this has been true of the U.S.A. as well. The drive exists not only in bureaucrats but in legislators as well.

The late Supreme Court Justice, Louis D. Brandeis, once observed, "Experience should teach us to be most on our guard to protect liberty when the government's purposes are beneficent. Men born to freedom are naturally alert to repel invasion of their liberty by evil-minded rulers. The greatest dangers to liberty lurk in insidious encroachment by men of zeal, well-meaning but without understanding."

It is likely that no startling legislative changes in regard to medicine will take place in 1976 but once the elections are over the sluice gates of legal innovations will open wide and particularly so in the overall area of medical care. Justice Brandeis' words may not have been directed to this area but his warnings about the "insidious encroachment by men of zeal, well meaning but without understanding" and their danger to liberty are appropriate and should be kept in mind.

Non-ketotic Diabetes

CLINICAL QUOTE: *"The second interpretation of our results [that reflects our current view] begins by viewing diabetes mellitus as a disease made up of a continuous spectrum of individuals with varying degrees of glucose intolerance, with the severity of the hyperglycemia dependent upon each patient's degree of insulin resistance and/or deficiency. In this case, the primary lesion in diabetes is resistance to the action of insulin, and the physiologic response is to increase insulin secretion in an attempt to minimize hyperglycemia. However, the continuous need to maintain an increased secretion of insulin could lead to pancreatic exhaustion with the subsequent development of insulin deficiency. In this formulation, insulin resistance is the basic defect in non-ketotic diabetes, and insulin deficiency is viewed as a secondary phenomenon."* (Dr. Gerald M. Reaven, of Stanford University. See page 1.)

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LETTERS TO TRIBUNE

Contraception and the Heart

If Frances Goodnight's report (MT, Nov. 5) correctly reflects Dr. Louise Tyrer's (and Planned Parenthood's) response to the British paper on oral contraceptives and heart attacks, then that organization would do well to add biostatistical competence to their advisory panel. The British report, a so-called case-control study, by its very *nature cannot yield cause-and-effect* answers; yet, this is what Dr. Tyrer infers.

The number of factors which affect the incidence of heart attacks so confounds the role of oral contraceptive use that complex multivariate statistical methods must be used in the analysis of such data. In actuality, the report is based on a simplistic, wholly inappropriate statistical procedure. The authors themselves indicate that the confidence limits of the calculated relative risks are extremely large because of the small sample size, yet Dr. Tyrer quotes risk estimates ostensibly accurate to three significant figures.

This wholesale acceptance of an unconfirmed, flawed epidemiological study recalls Planned Parenthood's over-reaction a few years ago to the discredited Melamed cervical dysplasia study, and to other adverse reaction reports of equally low scientific caliber. One begins to wonder which side of the contraception problem Planned Parenthood *is on, these days.*

JOSEPH W. GOLDZIEHER, M.D.
Southwest Foundation for Research and Education
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"The Three Horsemen . . ."

Dr. Sackler in his fine column, "The Three Horsemen of Death," questions the attitude of the politicians who attack useful drugs and their manufacturers while leaving alcohol and nicotine unscathed. Does he not realize that enormous tax revenue is exacted by federal, state and city governments from booze and cigarets and that it would not do to assail these "holy cows" or if you will "golden calves"? Drugs produce no such direct revenues but make good copy that gives rise to grateful votes.

PAUL SINGER, M.D.
Summit, N.J.

The Stranglehold of the I.Q. *by Benjamin Fine, Doubleday & Company, Garden City, N.Y., $7.95*

"...A further biting indictment of the I.Q. tests is made by Dr. Mercer of California, who observes that if the I.Q. tests were abandoned, it would eliminate their misinterpretation and misuse in educational practice. It would make I.Q. scores irrelevant and unavailable. By abolishing I.Q. testing, educators would be forced to look beyond this convenient label and come to grips with the needs of children in all their individual complexities.

"Moreover, Dr. Mercer objects to the reference to I.Q. scores as "intelligence quotients," adding that it is archaic to accept as accurate the relationship between chronological age and mental age. The term "intelligence quotient," or I.Q. as it is known, has acquired a semimystical meaning, rendering it useless as an accurate scientific instrument.

"If used at all, I.Q. tests should, in all fairness, be standardized on similar sociocultural and ethnic backgrounds of the children tested. In that way, a child's score could be compared with other children of his own culture and background. A pluralistic, sensitive interpretation of the meaning of how children perform on all standardized tests would prove a sounder basis, than is now possible through I.Q. tests, to determine the youngster's ability.

..."It is essential, if education is to be improved in this country, and if all children are to receive equality of opportunity, to discontinue I.Q. testing and to weaken the hold it has upon the *educational world.*

"The I.Q. score has become a badge of accomplishment, a medal of honor, a symbol of elitism. Parents boast about the I.Q. scores their children receive as though this was the most important part of the entire educational system.

"But you can't blame the parents. They have been brainwashed and oversold on the value and importance of the I.Q. and have accepted the assessment of teachers, guidance counselors, or psychologists that a high I.Q. score is a magic opening for their children to academic and worldy success."

M.D. Charged with Murder Urges New Euthanasia View

Continued from page 1

arrested for refusing to force-feed several unconscious, terminally-ill patients in his care. The charge was not malpractice—but murder. Although he has already been reinstated at the hospital, he is still under indictment pending investigation of the cases in question.

He also told the 300 participants at the day-long conference that the misleading term "euthanasia" applied to patients "whose personalities are irretrievably lost and who are being kept 'alive' artificially" should be dropped altogether and replaced by an "objective new term."

Demonstration Outside

While he and others spoke, a group of young demonstrators outside the Time-Life building carried signs that read "Death Be Not Proud" and "Euthanasia is Murder." In an impromptu interview with MEDICAL TRIBUNE, they all asserted that people like Dr. Haemmerli and other "euthanasia advocates" were part of a movement to eradicate "meaningless" members of society—unwanted fetuses, the deformed, the aged, and the terminally ill.

Nothing, according to Dr. Haemmerli, could be further from the truth.

In his definition of death, he called for a broadening of the "Harvard criteria" for cerebral death to include patients "whose brains have died but who have preserved their spontaneous respiration and can be treated [with IV feeding, etc.] in normal wards."

A patient is "humanly dead," he contends, when consciousness and personality are "permanently" and "irretrievably lost," even though spontaneous respiration may continue because deeper brain structures are only partially affected. This kind of patient, he pointed out, is far more common in everyday practice than the patient in the Harvard criteria.

The Harvard criteria, he noted, include irreversible unconsciousness, accompanied by 1) failure to respond to sensory or sensitive stimuli, 2) limp extremities without reflexes, 3) large pupils not reacting to light, 4) a swift fall in blood pressure after removal of circulatory support, and 5) absence of spontaneous respiration.

However, these criteria for death were established only in reference to transplant surgery and the organ-donor situation, Dr. Haemmerli said. "Thus it is not death, or the death of the brain in general which is defined, but only a specific death situation," something the lay press "often disregards."

Prolonging Death

Extraordinary measures such as force-feeding only prolong a terminal patient's death rather than his life, Dr. Haemmerli said. They serve no therapeutic purpose in the terminal disorder itself. Discontinuing these measures, he told a special press conference, is the same as discontinuing an antibiotic that proves ineffective against a given organism. "Stopping a machine is no different, just more dramatic."

Even if a permanently unconscious patient can feel or realize anything, it is "the cruelest torture" to prolong their helpless suffering by artificial means, he told the press. To illustrate, he displayed a photograph of a patient similar to those whom he refused to continue force-feeding. The photo showed an 89-year-old woman weighing 56 pounds, paralyzed and unconscious for over a year. "The right to die, or death with dignity," Dr. Haemmerli said, "is the right not to suffer like this."

The physician's chief responsibility to such patients "is an adequate period of observation of the course of the disease, which supplements the diagnosis of the primary disease by showing whether the patient recovers or gets worse after commencement of treatment," Dr. Haemmerli stressed. This, he noted, "rules out errors of diagnosis with regard to irreversibility [of unconsciousness]."

In the case of heart arrest, observation for less than an hour is sufficient, he said, while failure of the brain with loss of respiration takes a few days, or, very occasionally, weeks. In brain failure with continued respiration, "weeks or often months are necessary."

Legal Redefinition

What is the physician's duty to patients who survive vegetatively as "apersonal, acerebral physiological torsi?" To keep them alive becomes inhumane; to pull the plug may bring criminal or malpractice charges. The solution, Dr. Haemmerli suggested, is to legally redefine the doctor's duty to all his patients in terms of his motivation, rather than the action taken. Dr. Haemmerli told the press he believes the Hippocratic Oath is outmoded and proposed tentatively the following new definition of the physician's duty:

"A doctor must exercise his profession humanely to the best of his knowledge and belief and in his patient's best interests. He must treat his patient in the same way as he would wish his father, mother, wife, child, or himself to be treated by another doctor if in the same medical situation as the patient concerned."

Thus, "in the case of termination of action taken to prolong the life of the patient whose brain is dead . . . what is important to the doctor is not his motivation for terminating the action, but his primary motivation with regard to the patient.

"Relief of suffering of incurably sick persons, such as those suffering from cancer with metastases, and of other grave symptoms . . . is not considered by doctors as euthanasia, but as their obvious professional duty."

Current definitions, he observed, are based on intervention and "always describe an action," i.e., preserving and prolonging life and/or health, curing, or relieving suffering. However, in modern practice, "relieving suffering often means shortening life, either by interrupting treatment which has been begun, by not beginning any treatment, or by administering analgesic drugs in adequately large doses" over an extended period, Dr. Haemmerli said.

Defining the doctor's duty in terms of action has created a medical as well as a legal problem, he added. In medical school, the doctor is taught to act. "He is not trained in omitting to act. A young doctor feels therefore action to be 'good' and not acting to be 'bad.'" This notion, he suggested, would be corrected if the doctor's duty were based on his motivation to enhance the patient's well-being, even if this means to refrain from prolonging biologic death.

Stressing the importance of motivation in redefining the doctor's duty, Dr. Haemmerli compared the dying patient to a house on fire and the doctor to a fireman. If the fireman is unable to extinguish the blaze after trying everything in his power, is he guilty of arson for letting the house burn to the ground?

Doctor Protection

Based on these observations, the Swiss physician called for the abolition of the term *euthanasia* from medical practice. Problematic distinctions between "active" and "passive" euthanasia, public misunderstanding of the word, its socially stigmatized connotations, and the lack of a reliable terminology for classifying the various forms of what is known collectively as euthanasia are imperatives for deleting the word from the physician's lexicon, he said.

"It may perhaps not be necessary to give a legal definition to 'passive euthanasia' and make it lawful, provided the doctor's professional duty and human death are clearly defined," Dr. Haemmerli concluded. "A legal definition of the doctor's professional duty should make legal protection for the doctor possible."

However, in any future legal discussion of euthanasia and in the establishment of new definitions, the doctor and nursing staff, as well as public opinion, should be consulted before any new law is written, he said.

If there is dignity to human life and if death is its inevitable outcome, it is also the doctor's duty, Dr. Haemmerli suggested, to change the public image of death as "an unconscious person with tubes protruding from all orifices" to that of death with dignity occurring "as a natural course of events," and shared openly by all people, along with birth and aging.

Bicycling for the Blind

Blind cyclist Catherine Hannas crosses the finish line in tandem with champion cyclist Bob Panter, after a 495-mile ride from Adelaide to Melbourne, Australia. The six-day journey involving six blind and six sighted riders was sponsored to promote cycling activities among the blind.

Legislative Efforts

► Also speaking at the conference on the legal aspects of euthanasia were George Annas, Director of the Center for Law and Health Sciences, Boston University School of Law, and Raymond Ewell, an Illinois state legislator.

Citing precedents such as the "Good Samaritan" law and the Uniform Anatomical Gift Act, Mr. Annas concluded, "If you don't change the attitudes of physicians and patients, new laws [regarding euthanasia] won't change their actual behavior."

The Good Samaritan law exempts physicians from most malpractice charges, he said, but did not cause an increase in the number of doctors stopping at traffic accidents. Nor does the UAGA prevent many families from refusing to allow deceased members to donate their organs even though the donor's intent is legally binding.

He also noted that "in our society, the physician makes most of the tough health decisions. Instead, patients should regain the right to make these decisions," including the right to die. Preserving this right is the intent of the Euthanasia Educational Council's "Living Will," a document available at the conference, stating the signee's wish not to be kept alive "by artificial means."

Mr. Ewell, who represents a district in Chicago, discussed his recent attempts to introduce "death with dignity" legislation in Springfield, and the "appalling lack of understanding" that ensued during debates. The bills, he said, specified that the decision to die was to be made by no one other than the person dying, yet "people see euthanasia as disposing of unwanted members of society." Both bills were soundly defeated in the legislature.

Mr. Ewell concluded that "as long as we're a society that believes in miracles, you'll have a difficult time getting doctors to pull the plug." As the most vivid example of public misunderstanding and apprehension about the euthanasia issue, Mr. Ewell quoted one of many telegrams he received opposing his legislation.

"We are against youth in Asia," the message read.

FDA Chief Seeks To Improve All Phases of Agency's Work

Text of interview with FDA Commissioner, Dr. Alexander M. Schmidt, by Dr. Arthur M. Sackler, MEDICAL TRIBUNE publisher.

Q. The FDA has made significant progress in raising the scientific caliber of its staff in recent years. Can this progress be maintained?

A. I certainly hope so. Success in recruiting usually depends on several different things. One is an ability to find people who want to do what needs doing, and a second is an appropriate reward system.

The question arises as to why good scientists, why good people, would *want* to come and work with FDA. One of our current problems is that we have an inadequate professional milieu in which topflight scientists could come and remain, and remain stimulated and excited by what they do for a long period of time. Some of our professionals complain that it is hard to remain excited professionally in a light green office 16 feet by 10 feet, largely doing research on other people's research.

So the question comes up as to whether or not more in-house science, which we need for many reasons, would be an inducement for people to come; whether our interaction with advisory committees, which is increasing, will help people keep up professionally.

Of course, the salary situation is not good. When we can offer somebody only half what he is already making, recruiting is very difficult.

Q. Couldn't raising the consciousness of the public and the Congress to the financial sacrifices that your people are not only called upon to make, but actually do make, help improve the situation?

A. Yes. Public approbation is another form of reward, and it is true that the work our professionals do is among the most important that any professionals in this country do. They make decisions which are sometimes literally life-and-death decisions for large numbers of people. I am constantly amazed that we do have top notch people in the agency who are happy and productive. For these people, the professional spirit is internal in that they generate it themselves, which a professional should do. I think that is marvelous.

Q. What is your current primary objective in the drug regulatory area?

A. One objective is to be more certain that we are basing our regulatory decisions on the best possible science. This is why we are increasing our use of advisory committees. We are also increasingly having open public hearings on scientific issues; we are involving NIH and other groups formally in our work; we are putting safety data almost immediately on public display and inviting comment on them. All these things are intended to improve our scientific base.

Q. Wouldn't more support of scientific communication and fewer legislative hearings help achieve a better FDA contribution to public health?

A. First, I would say that Congressional oversight of FDA is important and proper. Having said that, I will turn around and say we have far too many hearings and oversight inquiries. Some that occupy our time are not as productive, in my view, as other endeavors might be. So my answer must be, "yes." We could spend our time more in the scientific arena, and less in the political arena.

Q. With the doctor-patient relationship so important in the therapeutic process, should not FDA be acting to improve that relationship?

A. Well, we certainly shouldn't be doing anything to disrupt it. Whether it is our job to work actively at the interface to improve it, I am not sure; because, you see, you sometimes and others have complained that we improperly get into the practice of medicine. I am not sure the doctor-patient interface is an area we should actively be working in except to be sure that the physician and his or her patient both are fully educated about drugs.

Q. You have raised the question of the FDA's function. Could I ask a series of questions at this point, because FDA is involved in so many areas other than drug regulation.

Could you define which of the following areas of FDA action are actually based on its legislative mandate: (1) Does the FDA have a mandate to direct therapeutics in medical practice?

A. No.

Q. (2) Was the FDA established to control therapeutic drug research?

A. No, not originally, but some control was added to our list of things to do by Congress in 1962.

Q. To control all therapeutic research or just that by pharmaceutical companies?

A. I would have to go back to the 1962 amendments to see exactly what the words were. The FDA is to regulate that clinical investigation done to obtain the substantial evidence for safety and efficacy presented to us by investigators that are selected by the drug companies . . .

Q. That is, by the drug firm . . .

A. No, I take that back, because it covers more than drug firms. We are concerned with research done under the investigational new drug application (IND).

Q. But if a physician is doing research . . .

A. Not under an IND?

Q. That's correct, not under an IND, then he doesn't come under your regulations?

A. That would be correct, but the question I would immediately ask is, is this research on a new drug? Because if it is, then it should be under an IND.

Vicki Lefcourt Photo

DR. SCHMIDT

Q. Even if he discovered a natural substance, an extract or new substance, for example, such as Fleming's in relationship to his work with penicillin?

A. Well, clearly we have not been active in the area you are talking about now; and clearly, unless the law were changed, we would not get into that area unless interstate commerce were involved.

Q. (3) Is the FDA an educational body?

A. Yes.

Q. By mandate?

A. Yes.

Q. (4) Is it a licensing body?

A. Yes.

Q. Aside from licensing of drugs, does it have the right to license physicians to do or not do research?

A. Yes and no. We do not actively license researchers; we can defrock them for fraudulent research.

Q. (5) Is the FDA an economic body?

A. A lot of people, particularly now, are saying that we do have a very great economic impact with our regulations. Practically speaking, our regulations do have an economic effect about which we must be aware, but in the sense you are asking the question, clearly not. We must write inflation impact statements, for example, which I think we should. But in terms of the pricing of drugs, or reimbursement policies and that sort of thing, our involvement is indirect, if at all.

Q. (6) Does the FDA's mandate run to publishing? I raise the question because of your *Bulletin*.

A. We have authority to publish educational and technical materials.

Q. (7) Is it a prosecutory body?

A. I don't know what you mean by that.

Q. There have been situations in which the failure of a manufacturer to go along with an FDA decision in respect to a drug has been followed by intense regulatory review or entry of inspectors into their plants.

A. Let me be very clear. The Food, Drug and Cosmetic Act is a criminal statute and we enforce it. We are a law enforcement agency. This is something I think a lot of people don't appreciate; in a very real sense, we are policemen. When we promulgate regulations based on criminal statute, they carry the force of law, and we prosecute violations.

Q. No, I am not referring to a direct violation. I am referring to the use of the inspection vehicle as a form of retribution for non-cooperation.

A. I would consider that a very serious charge. If anybody says that happens, I want to know immediately the details of the charge. Such activity would be highly improper.

Q. (8) Is the FDA a judicial body?

A. Well, again, your questions and your phrases have meaning for you, but I am not sure what you mean. There is a judicial branch of government, and in the strict definition of the term, no, we are more prosecutors than we are judges. But, again, I am not sure I know what you mean.

Q. (9) Is it a legislative body?

A. No.

Q. The reason I have asked those questions is that historically our government has separated these functions and it would appear that the FDA in its operations has not separated the functions.

A. Well, again, I would say that you have drawn a conclusion. I would have to have evidence on which you base your conclusion to comment satisfactorily. I have looked very carefully at this area, because I am well aware that from the framing of our government 200 years ago, there has been concern about what some people have called the fourth branch of government—the executive agency. Clearly, FDA is a member of the executive branch of government. We implement legislation and we interact daily with the courts. And we implement court decisions. I think one has to be fairly sophisticated and thoughtful in order to separate out those three functions that admittedly are often intertwined. To say that we can do our job without rubbing up against other branches of government to some extent is to be naïve.

Q. Does this not make it imperative, therefore, for the FDA to be as nonpartisan in its operations as possible?

A. Absolutely. But the biggest block to that is outside the agency, not inside.

Q. Does not the concept of drug regulation imply increasing the development and flow of new, important therapeutic agents as well as holding back potentially hazardous ones?

A. Without any question. We have the dual responsibility to impede bad drugs from getting on the market, and not to impede good drugs from getting on the market. Having an active advocacy function for drugs, however, would bother me. We should be as dispassionate as possible.

To Continue Next Issue

Ismelin® sulfate
(guanethidine sulfate)

Esimil®

guanethidine monosulfate	10 mg
hydrochlorothiazide	25 mg

WARNING (Esimil)
This fixed combination drug is not indicated for initial therapy of hypertension. Hypertension requires therapy titrated to the individual patient. If the fixed combination represents the dosage so determined, its use may be more convenient in patient management. The treatment of hypertension is not static, but must be reevaluated as conditions in each patient warrant.

INDICATIONS
Ismelin
Moderate and severe hypertension either alone or as an adjunct.
Esimil
Hypertension. (See box warning above.)
CONTRAINDICATIONS
Guanethidine: Known or suspected pheochromocytoma; hypersensitivity; frank congestive heart failure not due to hypertension; use of MAO inhibitors.
Hydrochlorothiazide: Anuria; hypersensitivity to this or other sulfonamide-derived drugs. The routine use of diuretics in an otherwise healthy pregnant woman with or without mild edema is contraindicated and possibly hazardous.
WARNINGS
Antihypertensives are potent drugs and can lead to disturbing and serious clinical problems. Physicians should be familiar with all drugs and their combinations before prescribing, and patients should be warned not to deviate from instructions.
Guanethidine

Warn patients about the potential hazard of orthostatic hypotension, which can occur frequently and is most marked in the morning and is accentuated by hot weather, alcohol, or exercise. To help prevent fainting, warn patients to sit or lie down with onset of dizziness or weakness, which may be particularly bothersome during the initial period of dosage adjustment and with postural changes. The potential occurrence of these symptoms may require alteration of previous daily activity. Caution patients to avoid sudden or prolonged standing or exercise while taking the drug.

Concurrent use with rauwolfia derivatives may cause excessive postural hypotension, bradycardia, and mental depression.
If possible, withdraw therapy 2 weeks prior to surgery to reduce the possibility of vascular collapse and cardiac arrest during anesthesia. If emergency surgery is indicated, administer preanesthetic and anesthetic agents cautiously in reduced dosage and have oxygen, atropine, vasopressors, and IV solutions ready for immediate use to treat vascular collapse. Vasopressors should be used with extreme caution in patients on guanethidine because of the possibility of augmented response and the greater propensity for cardiac arrhythmias.
Dosage requirements may be reduced in presence of fever. Exercise special care when treating patients with a history of bronchial asthma, since their condition may be aggravated.
Hydrochlorothiazide
Use with caution in severe renal disease. In patients with renal disease, thiazides may precipitate azotemia. Cumulative effects of the drug may develop in patients with impaired renal function.
Thiazides should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte imbalance may precipitate hepatic coma.
Thiazides may be additive or potentiative of the action of other antihypertensive drugs. Potentiation occurs with ganglionic or peripheral adrenergic blocking drugs.
Sensitivity reactions are more likely to occur in patients with a history of allergy or bronchial asthma.
The possibility of exacerbation or activation of systemic lupus erythematosus has been reported.
Usage in Pregnancy
Guanethidine: The safety of guanethidine for use in pregnancy has not been established; therefore, this drug should be used in pregnant patients only when, in the judgment of the physician, its use is deemed essential to the welfare of the patient.
Hydrochlorothiazide: Usage of thiazides in women of childbearing age requires that the potential benefits of the drug be weighed against its possible hazards to the fetus. These hazards include fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions which have occurred in the adult.
Nursing Mothers
Thiazides cross the placental barrier and appear in cord blood and breast milk.
PRECAUTIONS
Guanethidine: The effects of guanethidine are cumulative over long periods; initial dose should be small and increased gradually in small increments. Use very cautiously in hypertensives with renal disease and nitrogen retention or rising BUN levels; coronary disease with insufficiency or recent myocardial infarction; cerebral vascular disease, especially with encephalopathy. Do not give guanethidine to patients with severe cardiac failure except with extreme caution.
In incipient cardiac decompensation weight gain or edema may be averted by the administration of a thiazide. Remember that both digitalis and guanethidine slow the heart rate.
Peptic ulcers or other chronic disorders may be aggravated by a relative increase in parasympathetic tone.
Amphetamine-like compounds, stimulants (eg, ephedrine, methylphenidate), tricyclic antidepressants (eg, amitriptyline, imipramine, desipramine) and other psychopharmacologic agents (eg, phenothiazines and related compounds), and oral contraceptives may reduce the hypotensive effect of guanethidine. Discontinue MAO inhibitors for at least one week before starting guanethidine.
Hydrochlorothiazide: Periodic determination of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals. Observe patients for clinical signs of fluid or electrolyte imbalance (hyponatremia, hypochloremic alkalosis, and hypokalemia). Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Medication such as digitalis may also influence serum electrolytes. Warning signs are dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbance such as nausea or vomiting.
Hypokalemia may develop with thiazides as with any other potent diuretic, especially during brisk diuresis, when severe cirrhosis is present, or during concomitant administration of steroids or ACTH.
Interference with adequate oral intake of electrolytes will also contribute to hypokalemia. Digitalis therapy may exaggerate metabolic effects of hypokalemia especially with reference to myocardial activity.
Any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease). Dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy is water restriction rather than administration of salt, except in rare instances when the hyponatremia is life-threatening. In actual salt depletion, appropriate replacement is the therapy of choice.
Hyperuricemia may occur or frank gout may be precipitated in certain patients. Insulin requirements in diabetic patients may be increased, decreased, or unchanged. Latent diabetes may become manifest during thiazide administration.
Thiazide drugs may increase the responsiveness to tubocurarine. The antihypertensive effects of the drug may be enhanced in the post-sympathectomy patient. Thiazides may decrease arterial responsiveness to norepinephrine. This is not sufficient to preclude effectiveness of the pressor agent for therapeutic use.
If nitrogen retention indicates onset of progressive renal impairment, consider withholding or discontinuing diuretic therapy.
Thiazides may decrease serum PBI levels without signs of thyroid disturbance.
ADVERSE REACTIONS
Guanethidine: *Frequent reactions due to sympathetic blockade*—dizziness, weakness, lassitude, syncope. *Frequent reactions due to unopposed parasympathetic activity*—bradycardia, increase in bowel movements, diarrhea (may be severe and necessitate discontinuance of the drug).
Other common reactions—inhibition of ejaculation, fluid retention, edema, congestive heart failure. *Other less common reactions*—dyspnea, fatigue, nausea, vomiting, nocturia, urinary incontinence, dermatitis, scalp hair loss, dry mouth, rise in BUN, ptosis of the lids, blurring of vision, parotid tenderness, myalgia, muscle tremor, mental depression, chest pains (angina), chest paresthesias, nasal congestion, weight gain, and asthma in susceptible individuals. Although a causal relationship has not been established, a few instances of anemia, thrombocytopenia and leukopenia have been reported.
Hydrochlorothiazide: *Gastrointestinal*—anorexia, gastric irritation, nausea, vomiting, cramping, diarrhea, constipation, jaundice (intrahepatic cholestatic), pancreatitis. *Central Nervous System*—dizziness, vertigo,

(Brief prescribing information continued on next page)

CIBA

In moderate hypertension...

"Guanethidine and methyldopa proved to be equally effective in controlling moderately elevated standing diastolic blood pressure. However, reduction of mean blood pressure to acceptable levels was achieved more frequently with guanethidine than with methyldopa"[1]

1. Tarpley EL: Controlled trial of guanethidine and methyldopa in moderate hypertension. *Curr Ther Res* 16:1187-1196, 1974.

**All patients also received concomitant therapy with hydrochlorothiazide.*

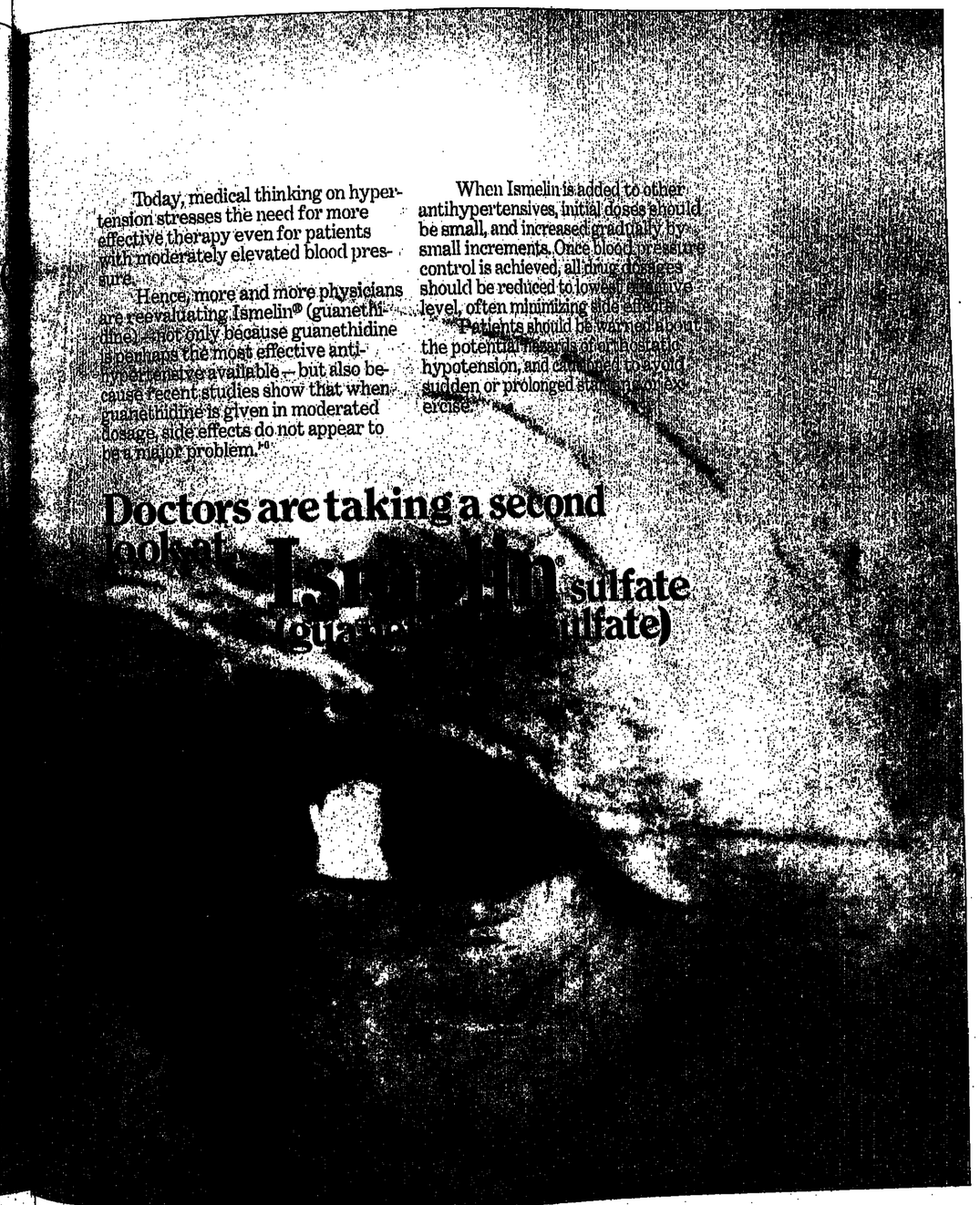
Today, medical thinking on hypertension stresses the need for more effective therapy even for patients with moderately elevated blood pressure.

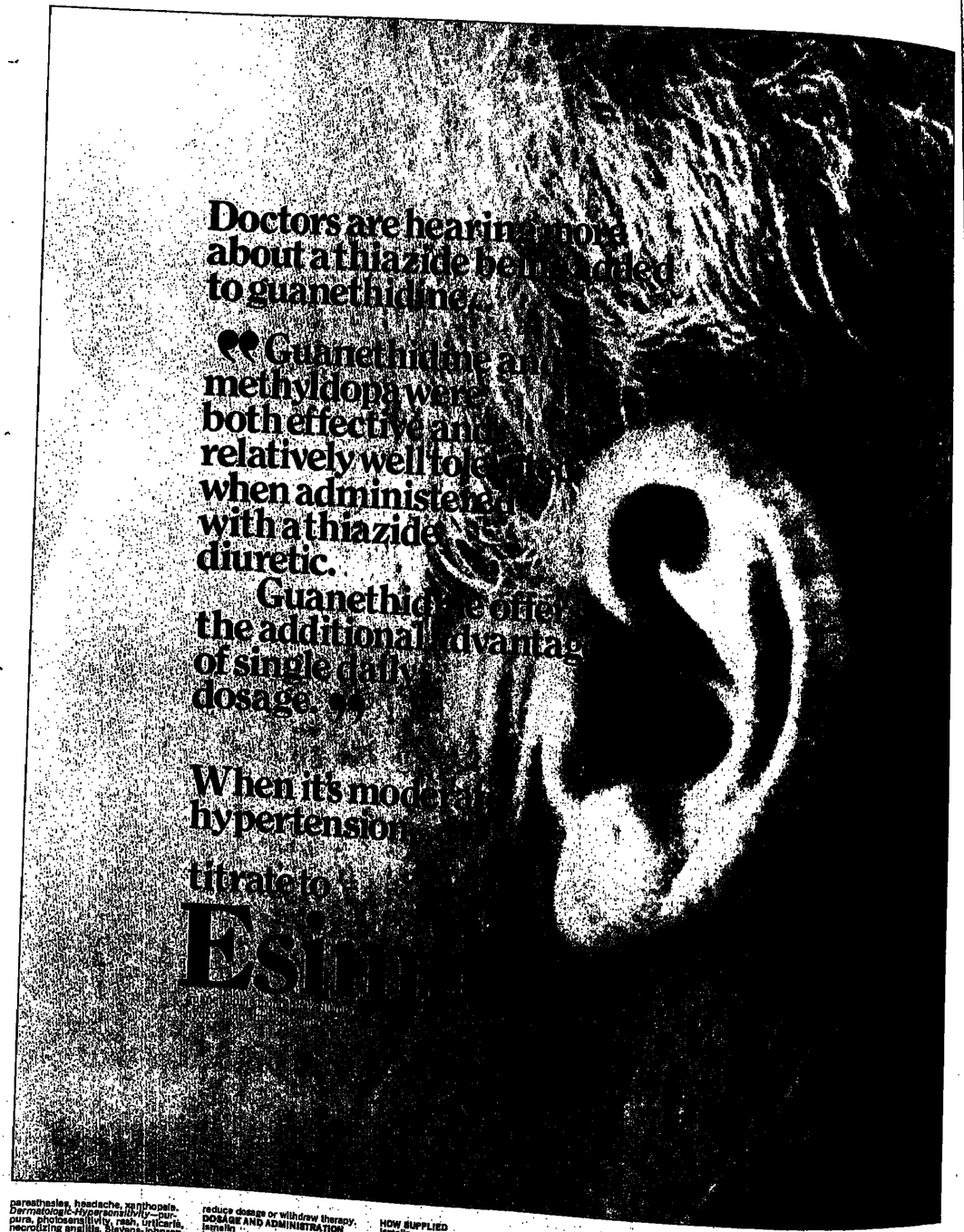
Hence, more and more physicians are reevaluating Ismelin® (guanethidine) – not only because guanethidine is perhaps the most effective antihypertensive available – but also because recent studies show that when guanethidine is given in moderated dosage, side effects do not appear to be a major problem.[1]

When Ismelin is added to other antihypertensives, initial doses should be small, and increased gradually by small increments. Once blood pressure control is achieved, all drug dosages should be reduced to lowest effective level, often minimizing side effects.

Patients should be warned about the potential hazards of orthostatic hypotension, and cautioned to avoid sudden or prolonged standing or exercise.

Doctors are taking a second look at Ismelin® sulfate (guanethidine sulfate)





paresthesias, headache, xerophoria. *Dermatologic-Hypersensitivity*—purpura, photosensitivity, rash, urticaria, necrotizing angiitis, Stevens-Johnson syndrome, and other hypersensitivity reactions. *Hematologic*—leukopenia, agranulocytosis, thrombocytopenia, aplastic anemia. *Cardiovascular*—orthostatic hypotension may occur and may be potentiated by alcohol, barbiturates, or narcotics. *Other*—hyperglycemia, glycosuria, hyperuricemia, muscle spasm, weakness, restlessness. Whenever adverse reactions are moderate or severe, reduce dosage or withdraw therapy.

DOSAGE AND ADMINISTRATION

Esimil
Initial dosage should be low and increased gradually by small increments. *Before starting therapy, consult complete product literature.*

Esimil
As determined by individual titration. (See box warning.)

Before starting therapy, consult complete product literature.

HOW SUPPLIED

Esimil
Tablets, 10 mg (pale yellow, scored) and 25 mg (white, scored) bottles of 30, 60, 100 and 1000.

Esimil
Tablets (white, scored), each containing 10 mg guanethidine monosulfate and 25 mg hydrochlorothiazide; bottles of 30, 60 and 100.

CIBA Pharmaceutical Company
Division of CIBA-GEIGY Corporation
Summit, New Jersey 07901

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The Other Side Speaks

Letters Differing with Dr. Lasagna on Treatment of "Colds" and with Dr. Sackler's Column

MEDICAL TRIBUNE (Nov. 19, 1975) published a letter by Dr. Louis Lasagna, a leading pharmacologist, stating he believed ". . . most patients with upper respiratory complaints go to see doctors suffering from a combination of cough, stuffed nose, post-nasal drip, swollen glands in the neck, earache, etc.—in other words, from secondary bacterial complications of the common cold." He asked: "If this is the case, then the prescribing of an antibiotic is not wrong; rather the question is only: what antibiotic would be best?" He asked that MEDICAL TRIBUNE solicit responses from physician readers.

In the same issue, Dr. Arthur M. Sackler described how President Ford was given an antibiotic for the lingering effects of a cold and suggested what's good enough for the President of the United States "is good enough for our patients."

In previous issues, MEDICAL TRIBUNE has published representative selections of the overwhelming majority of letters, supporting the attitude of Drs. Lasagna and Sackler.

In this issue we publish the minority report: comments that disagree with their views.

On "Colds and Antibiotics," two points must be made. First, "secondary bacterial complications of the common cold" justifying routine use of antimicrobials have not been established. Secondly, I sympathize with your feelings and respect your opinion, but decry any rationale that "What's good enough for the President of the United States is good enough for our patients, the citizens of the United States."

Please publish these two glaring objections to this approach to therapy.

J. S. FABIAN, M.D.
Lieutenant Commander, MC USNR
Department of Medicine
Naval Aerospace & Regional Medical Center
Pensacola, Fla.

For the past seven years I have been practicing at the University Health Service here. I believe your conclusions are erroneous. In our experience, the symptoms which you have described as secondary bacterial complications of the common cold are in fact primary symptoms of a great number of viral infections.

Under those circumstances, we practically never use antibiotics and merely give symptomatic therapy such as decongestants, fluids and aspirin, and antitussives where indicated. We adhere to the same high standards of medical practice as our academic staff.

SIDNEY R. MICHAEL, M.D.
Clinical Associate Professor of Medicine
University of Wisconsin
Madison, Wis.

In response to your request (MT, Nov. 19), I think that you will already know and agree with what I have to say.

There is, of course, no justification for antimicrobic therapy or prophylaxis for any viral infection. The matter was emphasized in almost all my consecutive Annual Reviews of Infections since 1935, especially regarding viral respiratory tract infections.

The group (colds, rhinitis, ARD, flu, viral pharyngitis), as you know, comprises the commonest of all minor ailments. "Treated they last two weeks; untreated, a fortnight." The aphorism still holds.

Secondary bacterial invasion occurs in about 1% of victims, but only pneumococcal and hemolytic streptococcal infections respond to therapy. The change from an early watery discharge to an opaque viscid "purulent" one containing the normal flora often is mistaken for evidence of bacterial invasion and leads to unnecessary therapy.

If cost were no object, routine roentgenography predictably would disclose unsuspected viral pneumonia in most victims of a "heavy" cold. Some of these are ambulatory, as I was three times. Traditionally, pneumonia during colds has always been ascribed wrongly to bacterial invasion.

In one recent article, 25% of a population with colds sought medical attention. (*JAMA* 227: 164, 1974). In others, two-thirds of 100 million Rx's for antimicrobics were prescribed unnecessarily for colds (*Brit. Med. J.* 3: 1, 1974), and they were "useless" in 89 children (*Med. J. Australia*, 1: 304, 1974). "Over-the-counter" sales total $1 billion annually (*Blue Cross Rev.* Feb., 1973). In one compilation, physicians prescribed antimicrobics for 60% of colds almost all needlessly (*Ann. Int. Med.* 76: 577, 1972) . . .

I could go on, but I'm sure you are well aware of the misuse. At least, those are my views of the matter. Physicians are not always to blame. Patients often demand "wonder drugs," and if one physician is brave enough to decline, another probably will submit to coercion. Physicians may be apprehensive and prescribe antimicrobics routinely as a mode of "defensive medicine," lest the 1% of untreated secondary infections end seriously.

Purists prefer the term antimicrobic to antibiotic (anti-bios = against life) of which the atom bomb is the best example. You may remember that I called attention to the redundancy of "human" volunteers.

HOBART A. REIMANN, M.D.
Professor of Medicine
Hahnemann Medical College & Hospital
Philadelphia

I believe that Dr. Lasagna's basic premises are unfounded, at least as they apply to this part of the country in this day and age. My experience is that many patients do visit a doctor's office for advice about uncomplicated coryza. You have ignored the fact that many, or most patients, now have employer-paid health benefits, so that little if any out-of-pocket expense is involved in coming to a doctor's office. Many of these patients also have "other people"-paid prescription plans which enable them to purchase medication for symptomatic relief much more cheaply if it is prescribed by a physician than if bought "over the counter." Finally, many employers require a note from a physician if an employee is away from work because of illness—another socio-economic reason for a visit to the doctor which otherwise wouldn't be required.

Two Sundays ago, I was "O.D." for the doctors who share my medical building, there supposedly to provide for urgent medical problems which could not wait until Monday. Of the patients seen, four had "colds." One was a mother, who had minimal symptoms, and who had brought her son, whose symptoms were practically gone. Another was a wife who "didn't want to bother" me and who had brought her husband who came because she made him. None of them required other than supportive treatment—no prescriptions were needed and none given. This is a rather typical occurrence for the reasons outlined above.

STANLEY SLATER, M.D.
Brooklyn, N.Y.

In the matter of antibiotics and "the common and not-so-common cold," your argument is intriguing, but I think it is sophistry.

The laboratory in our small, but accredited, hospital in a town of less than 7000 people is excellent. We can receive the Group A, B hemolytic streptococcus screening report the following morning and the sensitivity reports on other pathogens within 48 hours.

On the first visit of the average "cold" patient, then, is it unreasonable to get a throat culture and prescribe symptomatic medical treatment until the next or second day, when we will know whether the patient needs an antibiotic at all and, if so, what antibiotic?

As far as rheumatic fever and glomerulonephritis are concerned, according to the experts, no increased risk is encountered by delaying the use of antibiotics for Group A infections for one or two days or even six or seven days.

Laboratory tests cost money, yes, but so do prescriptions for antibiotics. In a large percentage of patients, where no antibiotic is indicated, these factors will cancel each other out, and we will avoid the needless risk of sensitizing patients to drugs they do not need and of increasing the resistance of bacteria to the presently-known and used antibiotics.

During the past 50 days here we have done 70 throat cultures. Only three of these were Group A streptococcus; 25 others showed other pathogens, not all of which, of course, were sensitive to the commonly used penicillin, ampicillin, or a cycline antibiotic.

Granted that this is a mining town where 2/3 of our patients are workers or dependents whose medical bills are paid as fringe benefits. This means that many of our patients come into our clinic at the drop of a handkerchief and may explain, in part, the lower incidence of pathogenic bacteria in our upper respiratory infections.

In many rural situations, physicians may not have access to good laboratory facilities. Here, there may be a better excuse for "shotgunning" with antibiotics. But even here in my practice I am in a distinct minority. It gets lonely at times and I sure get tired of arguing with, and explaining to, people why they don't need, and shouldn't get, antibiotics, least of all by injection (which seems to be a very popular method of dispensing penicillin here). Certainly prescribing antibiotics for every sneeze and sniffle is the path of least resistance.

Your "heartfelt observation: What's good enough for the President of the United States is good enough for our patients, the citizens of the United States" sounds like a good argument, but it may still be a specious one, reinforced more by the heart than the brain. Might I add that I personally believe the same thing about the Vitamin C you would have added to the President's therapeutic list? But that's a question still debated and as yet not definitely answered.

Perhaps I am a therapeutic nihilist. No, not quite! But definitely a medical conservative.

Your column "One Man . . . and Medicine" is excellent, Dr. Sackler. I enjoy it, especially the ones involving your travels, since I have always been touched with a trace of wanderlust.

THOMAS G. HARVEY, M.D.
New Cornelia Hospital
Ajo, Ariz.

In reply to your editorial on antibiotics for the common cold, may I say that your broad, unfair generalizations about the appropriateness of the opinions of "officials, etc." are outdone only by your uncritical logic, references and clinical interpretations.

THOMAS B. CRUDEN, M.D.
Charleston, S.C.

It was embarrassing to read Dr. Lasagna's unsupported and clearly unsupportable assertion that "cough, stuffed nose, post-nasal drip, swollen glands in the neck, earache" constitute secondary bacterial complications of the common cold. Medical experience simply shows that some colds are worse than others and the overwhelming majority of patients with the symptoms described by Dr. Lasagna turn out to have, even on the most meticulous study, viral upper respiratory infections which do not respond to antibiotics.

What is even more important and more embarrassing is that Dr. Lasagna suggests that this medical question can be solved by soliciting uncontrolled observations from clinicians like me all around the country when the question is so easily amenable to proper scientific investigation.

JAMES S. BERNSTEIN, M.D.
Rockville Centre, N.Y.

Fifteen scientists from three countries recently won the first Awards in Cancer Immunology sponsored by the Cancer Research Institute, Inc., New York. Recipients, from left to right, included Dr. Hans O. Sjogren, dept. of medical microbiology, Univ. of Lund, Lund, Sweden; Dr. Robert J. Huebner, chief, viral carcinogenesis branch, NIH, Bethesda, Md.; Dr. Lloyd J. Old, vice president and associate director, Sloan-Kettering Institute for Cancer Research, New York; Dr. Edward A. Boyse, Sloan-Kettering; Mr. Edward J. Foley, Schering Corp., Bloomfield, N.J.; Mr. Peter A. Gorer (for his late father, Dr. Peter A. Gorer); Dr. Edmund Klein, chief, dept. of dermatology, Roswell Park Memorial Institute, Buffalo, N.Y.; Dr. George Klein, dept. of tumor biology, Karolinska Institutet, Stockholm, Sweden; Dr. Richard T. Prehn, Professor of Pathology, University of Pennsylvania; Dr. Gertrud Henle, Children's Hospital, Philadelphia; Dr. Robert A. Good, president and director, Sloan-Kettering Institute for Cancer Research; Mrs. Helen C. Nauts, executive director, Cancer Research Institute, Inc.; Dr. Donald L. Morton, Professor of Surgery, School of Medicine, Univ. of Calif., Los Angeles; Dr. Ludwik Gross, chief, cancer research unit, Veterans Administration Hospital, Bronx, N.Y.; and Dr. Werner Henle, Children's Hospital, Philadelphia. Winners not pictured were Dr. Garri I. Abelev, N.F. Gamaleya Institute of Epidemiology and Microbiology, USSR Academy of Medical Sciences, Moscow, and Dr. Eva Klein, Karolinska Institutet. This "founders" group each received a monetary award and gold medal. In future years, only one or two scientists will be honored.

Inaugural Event: Cancer Immunologists Win Kudos

Dr. Sjogren (left) showed that tumor viruses can impart antigens to the surfaces of cells they render cancerous; Dr. Huebner (right), showed that viral antigens may persist after virus disappears.

Drs. Gertrud and Werner Henle elucidated the relation of the Epstein-Barr herpes virus to Burkitt's lymphoma, and to the self-limiting proliferative disease, infectious mononucleosis.

Dr. Boyse (left) helped found a school of immunogenetics concerned with the antigenic composition of cells; Dr. Good (right) pioneered research on the immune deficiencies of cancer patients.

Dr. George Klein (left), together with his wife, Dr. Eva Klein, has investigated tumor specific antigens in mice; Dr. Prehn (right) helped establish that cancer cells have specific antigens.

Dr. Gross, shown with his wife, helped establish the existence of specific antigens that can differentiate cancer from normal cells and so can elicit a cancer-destructive immune response.

The father of Mr. Gorer (left) was honored for his early immunogenetic analyses of the mouse; Dr. Old (right), along with Dr. Boyse, saw the importance of cell surface as the key to cellular control.

Dr. Edmund Klein (center, with hands folded) devised the first reproducibly effective immunological therapy for a human cancer. Mrs. Nauts (turning to side) founded the Cancer Research Institute.

Dr. Morton (second from right) saw that effective immunity against virus-induced tumors might fail to develop if infection occurs early in life and so gives rise to immunological tolerance.

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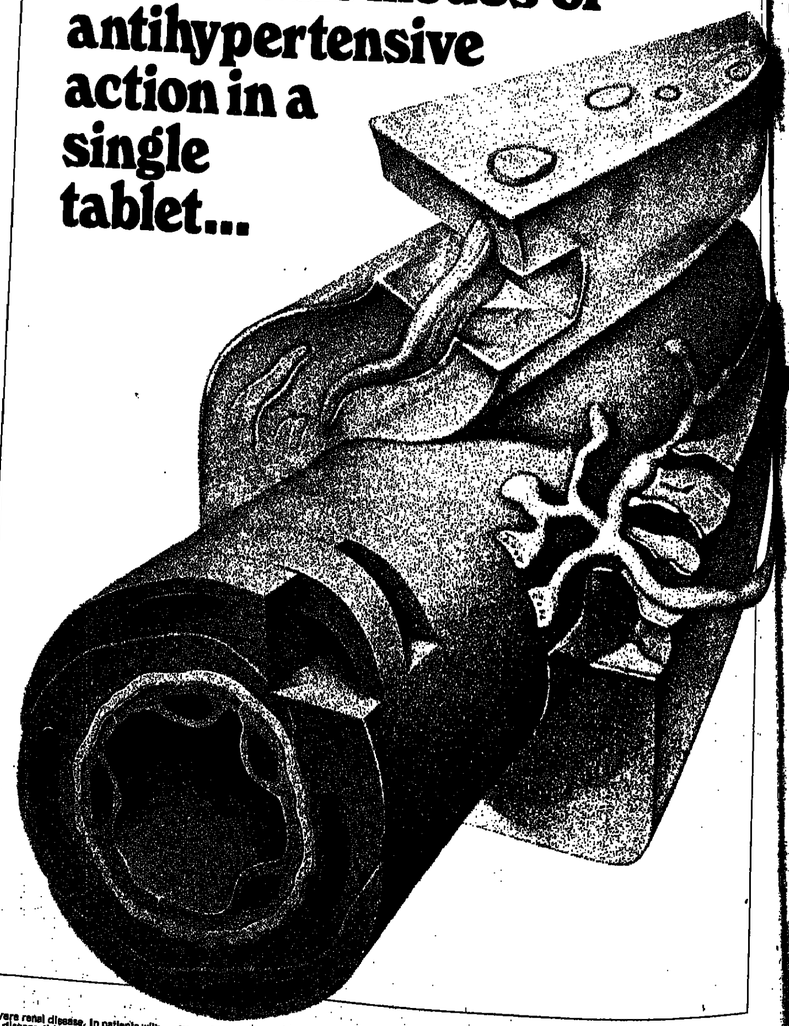

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Current clinical practice stresses the importance of achieving control of basic homeostatic mechanisms as the key to control of high blood pressure.[1]

Indeed, the landmark VA studies utilized three basic drugs to establish control of three homeostatic mechanisms.[2,3] These were control of fluid volume with hydrochlorothiazide, control of sympathetic activity with reserpine, and control of arteriolar tone with hydralazine. The study of 1967 concluded that most hypertensive patients could be successfully controlled with combinations of these basic drugs.[4]

Only Ser-Ap-Es provides control of three basic mechanisms—employing the same antihypertensives used in the VA studies. (In the VA studies, Ser-Ap-Es itself was not used. However, all the components of Ser-Ap-Es were used in varying combinations.)

And when the dosage of each component corresponds to the dosage preestablished by individualized titration, Ser-Ap-Es may prove more convenient and economical. Many patients will need no other medication.

Note: Use Ser-Ap-Es cautiously in patients with advanced renal damage or cerebrovascular accident. Discontinue at first sign of mental depression.

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WARNING
This fixed combination drug is not indicated for initial therapy of hypertension. Hypertension requires therapy titrated to the individual patient. If the fixed combination represents the dosage so determined, its use may be more convenient. In patient management. The treatment of hypertension is not static, but must be reevaluated as conditions in each patient warrant.

INDICATIONS
Hypertension. (See box warning.)

CONTRAINDICATIONS
Reserpine: Known hypersensitivity; mental depression (especially with suicidal tendencies); active peptic ulcer; ulcerative colitis; electroconvulsive therapy.
Hydralazine: Hypersensitivity; coronary artery disease; mitral valvular rheumatic heart disease.
Hydrochlorothiazide: Anuria; hypersensitivity to this or other sulfonamide-derived drugs. The routine use of diuretics in an otherwise healthy pregnant woman with or without mild edema is contraindicated and possibly hazardous.

WARNINGS
Reserpine: Use with extreme caution in patients with a history of mental depression. Discontinue at first sign of despondence, early morning insomnia, loss of appetite, impotence, or self-depreciation. Drug-induced depression may persist for several months after drug withdrawal and may be severe enough to result in suicide.
MAO inhibitors should be avoided or used with extreme caution.
Hydralazine: Hydralazine may produce in a few patients a clinical picture simulating systemic lupus erythematosus. In such patients hydralazine should be discontinued unless the benefit to risk determination requires continued antihypertensive therapy with this drug. Symptoms and signs usually regress when the drug is discontinued but residua have been detected many years later. Long-term treatment with steroids may be necessary.
CBC's, L.E. cell preparations, and antinuclear antibody titer determinations are indicated before and periodically during prolonged therapy with hydralazine or if the patient develops any unexplained signs or symptoms.
A positive antinuclear antibody titer and/or positive L.E. cell reaction requires that the physician carefully weigh the implications of the test results against the benefits to be derived from antihypertensive therapy with hydralazine.
Use MAO inhibitors with caution.
Hydrochlorothiazide: Use with caution in severe renal disease. In patients with renal disease, thiazides may precipitate azotemia. Cumulative effects of the drug may develop in patients with impaired renal function.
Thiazides should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte imbalance may precipitate hepatic coma.
Thiazides may be additive or potentiative of the action of other antihypertensive drugs. Potentiation occurs with ganglionic or peripheral adrenergic blocking drugs.
Sensitivity reactions are more likely to occur in patients with a history of allergy or bronchial asthma.
The possibility of exacerbation or activation of systemic lupus erythematosus has been reported.

Usage in Pregnancy
Reserpine: The safety of reserpine for use during pregnancy or lactation has not been established; therefore, the drug should be used in pregnant patients or women of childbearing potential only when, in the judgment of the physician, it is essential to the welfare of the patient. Increased respiratory tract secretions, nasal congestion, cyanosis, and anorexia may occur in neonates and breast-fed infants of reserpine-treated mothers since reserpine crosses the placental barrier and appears in maternal breast milk.
Hydralazine: The drug should be used only when, in the judgment of the physician, it is deemed essential to the welfare of the patient.
Hydrochlorothiazide: Usage of thiazides in women of childbearing age requires that the potential benefits of the drug be weighed against its possible hazards to the fetus. These hazards include fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions which have occurred in the adult. Thiazides cross the placental barrier and appear in cord blood.

Nursing Mothers
Thiazides appear in maternal breast milk.

PRECAUTIONS
Reserpine: Use cautiously in patients with history of peptic ulcer, ulcerative colitis, or gallstones (biliary colic may be precipitated).
Exercise caution when treating hypertensives with renal insufficiency. Use cautiously with digitalis and quinidine.
Intraoperative hypotension has occurred in hypertensive patients receiving rauwolfia preparations, but withdrawal of reserpine does not assure that circulatory instability will not occur in such patients.
Hydralazine: Use cautiously in suspected coronary artery or other cardiovascular disease, cerebral vascular accidents, and advanced renal damage. Postural hypotension may occur, and the pressor response to epinephrine may be reduced.
Peripheral neuritis, evidenced by paresthesias, numbness, and tingling, has been observed. Published evidence suggests an antipyridoxine effect and addition of pyridoxine to the regimen if symptoms develop.
Blood dyscrasias, consisting of reduction in hemoglobin and red cell count, leukopenia, agranulocytosis, and purpura, have been reported. If such abnormalities develop, discontinue therapy. Periodic blood counts are advised during prolonged therapy.
Hydrochlorothiazide: Periodic determination of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals. Observe patients for clinical signs of fluid or electrolyte imbalance (hyponatremia, hypochloremic alkalosis, and hypokalemia). Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Medication such as digitalis may also influence serum electrolytes. Warning signs are dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbance such as nausea or vomiting.
Hyponatremia may develop with thiazides as with any other potent diuretic, especially during brisk diuresis, when severe cirrhosis is present, or during concomitant administration of steroids or ACTH.
Interference with adequate oral intake of electrolytes will also contribute to hypokalemia. Digitalis therapy may exaggerate metabolic effects of hypokalemia especially with reference to myocardial activity.
Any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver diseases or renal disease). Dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy is water restriction rather than administration of salt, except in rare instances when the hyponatremia is life-threatening. In actual salt depletion, appropriate replacement is the therapy of choice.
Transient elevations in plasma calcium may occur in patients receiving thiazides, particularly in those with hyperparathyroidism. Pathological changes in the parathyroid gland have been reported in a few patients on prolonged thiazide therapy.
Hyperuricemia may occur or frank gout may be precipitated in certain patients. Insulin requirements in diabetic patients may be increased, decreased, or unchanged; latent diabetes may become manifest during thiazide administration.
Thiazide drugs may increase the responsiveness to tubocurarine. The antihypertensive effects of the drug may be enhanced in the post-sympathectomy patient. Thiazides may decrease arterial responsiveness to norepinephrine. This is not sufficient to preclude effectiveness of the pressor agent for therapeutic use.
If nitrogen retention indicates onset of progressive renal impairment, consider withholding or discontinuing diuretic therapy.
Thiazides may decrease serum PBI levels without signs of thyroid disturbance.

ADVERSE REACTIONS
Reserpine: Gastrointestinal—hypersecretion; nausea; vomiting; anorexia; diarrhea. *Cardiovascular*—angina-like symptoms; arrhythmias (particularly when used concurrently with digitalis or quinidine); bradycardia. *Central Nervous System*—drowsiness; depression; nervousness; paradoxical anxiety, nightmares; rare parkinsonian syndrome and other extrapyramidal tract symptoms; CNS sensitization (manifested by dull sensorium, dearness, glaucoma, uveitis, and optic atrophy). *Miscellaneous*—frequently nasal congestion; pruritus; rash; dryness of mouth; dizziness; headache; dyspnea; syncope; epistaxis; purpura and other hematological reactions; impotence or decreased libido; cyanis; muscular aches; conjunctival injection; weight gain; breast engorgement; pseudolactation; gynecomastia; rarely water retention with edema in hypertensive patients.
Hydralazine: Common—headache; palpitations; anorexia; nausea; vomiting; diarrhea; tachycardia; angina pectoris. *Less frequent*—nasal congestion; flushing; lacrimation; conjunctivitis; peripheral neuritis, evidenced by paresthesias, numbness, and tingling; edema; dizziness; tremors; muscle cramps; psychotic reactions characterized by depression, disorientation, or anxiety; hypersensitivity (including rash, urticaria, pruritus, fever, chills, arthralgia, eosinophilia, and, rarely, hepatitis); constipation; difficulty in micturition; dyspnea; paralytic ileus; lymphadenopathy; splenomegaly; blood dyscrasias, consisting of reduction in hemoglobin and red cell count, leukopenia, agranulocytosis, and purpura; hypotension; paradoxical pressor response.
Hydrochlorothiazide: Gastrointestinal—anorexia, gastric irritation, nausea, vomiting, cramping, diarrhea, constipation, jaundice (intrahepatic cholestasis), pancreatitis. *Central Nervous System*—dizziness, vertigo, paresthesias, headache, xanthopsia. *Dermatologic-Hypersensitivity*—purpura, photosensitivity, rash, urticaria, necrotizing angiitis, Stevens-Johnson syndrome, and other hypersensitivity reactions. *Hematologic*—leukopenia, agranulocytosis, thrombocytopenia, aplastic anemia. *Cardiovascular*—orthostatic hypotension may occur and may be potentiated by alcohol, barbiturates, or narcotics. *Other*—hyperglycemia, glycosuria, hyperuricemia, muscle spasm, weakness, restlessness. Whenever adverse reactions are moderate or severe, reduce dosage or withdraw therapy.

DOSAGE
As determined by individual titration (see box warning).
Usual dosage is 1 or 2 tablets t.i.d. For maintenance, adjust dosage to lowest patient requirement. When necessary, more potent antihypertensives may be added gradually in dosages reduced by at least 50 percent.

HOW SUPPLIED
Tablets (dark salmon pink, dry-coated), each containing 0.1 mg reserpine, 25 mg hydralazine hydrochloride, and 15 mg hydrochlorothiazide; bottles of 30, 60, 100 and 1000.

Consult complete literature before prescribing.

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Transfer Factor Scores as Coccidioidomycosis Therapy

Medical Tribune World Service

MEXICO CITY—Impressive results with transfer factor in patients with coccidioidomycosis refractory to treatment with amphotericin B were reported here at the 23rd Conference of the International Union against Tuberculosis.

Presenting the cumulative experience of a number of investigators who have formed the Coccidioidomycosis Cooperative Treatment Group (CCGT), Dr. J. Richard Graybill, Assistant Professor of Medicine, University of Texas, San Antonio, described the treatment as the "reconstitution of postdefense mechanisms with a white blood cell extract obtained from immune blood donors."

Responses Vary

A study population of 160 which included 82 healthy subjects (16 of whom had been clinically ill with coccidioidomycosis) and 78 patients with active coccidioidomycosis (34 with progressing pulmonary disease and 44 with extrapulmonary disease) were investigated to determine the type of immune deficits associated with active disease, as well as changes in three immunologic tests and clinical results after treatment. The tests were Mantoux skin test, lymphocytic blastogenesis, and migration inhibition factor (MIF). Forty-nine of the affected group (17 pulmonary and 32 disseminated) were treated with varying amounts of transfer factor.

Of the 34 pulmonary coccidioidomycosis patients, 23 had negative skin test while blastogenesis did not correlate with the skin test and MIF did. In the group of 44 with disseminated disease, the majority were skin test negative as well and neither blastogenesis nor MIF correlated with the Mantoux test very well. "This indicates," Dr. Graybill remarked, "that patients with active coccidioidomycosis may have complex defects of immune response. Also implicit in our data is that any patient can have any response pattern."

Forty-four patients were evaluated immunologically before and after treatment with transfer factor. Only eight of them had positive skin tests before but 24 converted from negative to positive after receiving the substance. The data for blastogenesis were similar but were said to have been even more impressive for MIF where only three of the 28 were positive prior to transfer factor and 21 converted after.

Clinically, 30 patients of the selected group of 49 (60%) were found to show distinct improvement following administration of transfer factor. Of these, the resolution of lesions was said to be dramatic, occurring within a few weeks of initiation of treatment, while in the remaining 18, improvement was gradual.

"However," Dr. Graybill pointed out, "conversions were not permanent. Often they lasted only a month and also did not occur after every dose. Sometimes only one of the three tests converted. As far as clinical improvement was concerned, it was not consistent either or directly correlated to conversion of a specific immune parameter. Likewise, it was not permanent and required additional transfer factor to be sustained."

A prospective controlled trial, indicated as being urgently needed to resolve the clinical controversy over transfer factor, has been designed by the CCGT and is now in a pilot phase.

The members of the CCGT include the N.I.H. and 11 institutions in Arizona, California, and Texas.

One Man . . . and Medicine

ARTHUR M. SACKLER, M.D.,
International Publisher, Medical Tribune

Because Dr. Sackler's interview with Food and Drug Administration Commissioner, Dr. Alexander M. Schmidt, is being published in this issue, his regular column will not appear—Editor.

FDA Chief Stresses Law Enforcement Role

Continued from page 1

ler and others had complained that the FDA improperly gets "into the practice of medicine" and said: "I am not sure the doctor-patient interface is an area we should be actively working in except to be sure that the physician and his or her patient are fully educated about drugs."

However, Commissioner Schmidt emphasized that "The Food, Drug and Cosmetic Act is a criminal statute and we enforce it. We are a law enforcement agency . . . in a very real sense we are policemen. When we promulgate regulations based on criminal statute, they carry the force of law, and we prosecute violations."

'Too Many Hearings'

Asked if more scientific communication and fewer legislative hearings would not help achieve a better FDA contribution to the nation's health, Commissioner Schmidt said that while Congressional "oversight" of FDA was important and proper, "we have far too many hearings and oversight inquiries." He felt some such hearings are not as productive as other efforts might be. "We might spend more of our time in the scientific arena and less in the political arena," he said.

Somewhat surprisingly, in view of his emphasis on its law enforcement role, Dr. Schmidt said that "without any question" FDA should contribute to the development of new drugs. "We had the dual responsibility to impede bad drugs from getting on the market, and not to impede good drugs from getting on the market."

However, as Dr. Schmidt saw it, the FDA role in developing better drugs was a limited one. "Having an active advocacy function for drugs would bother me. We should be as dispassionate as possible."

Dr. Schmidt described one of his primary objectives in drug regulation as being "more certain that we are basing our regulatory decisions on the best possible science." To that end, he pointed out that the FDA has increased its use of advisory committees and of public hearings on scientific issues, had involved the National Institutes of Health and other groups in their work, and was publicly displaying safety data almost immediately. "All these things are intended to improve our scientific base."

No Therapeutic Mandate

In discussing the FDA's function in response to a series of delineating questions from Dr. Sackler, Dr. Schmidt said that the FDA had no mandate to direct therapeutics in medical practice, did have some control over therapeutic drug research and clinical investigations of the safety and efficacy of drugs since 1962.

He also described the FDA as educational, authorized to publish educational and technical material. While describing the agency as a law enforcement body, he denied it also had a judicial character. ". . . in the strict definition of the term, no, we are more prosecutors than judges," said the FDA Commissioner.

In demurring, Dr. Schmidt said that he was not certain what Dr. Sackler's question—"Is the FDA a judicial body?"—meant.

Varied Functions Intertwine

When Dr. Sackler pointed out that his questions were based on the fact that the judicial and prosecutory functions of government had always been separate, Dr. Schmidt responded that he recognized "there has been concern about what some people have called the fourth branch of government—the executive agency."

However, he went on to say, "Clearly, FDA is a member of the executive branch of government. We implement legislation and we interact daily with the courts. And we implement court decisions. I think one has to be fairly sophisticated and thoughtful in order to separate out those three functions that admittedly are often intertwined."

When Dr. Sackler asked if the FDA should not be as nonpartisan in its operations as possible, Dr. Schmidt replied, "Absolutely! But the biggest block to that is outside the agency, not inside."

Need for Professionals

One of the problems of the FDA, said Dr. Schmidt, was getting good professional people to come to work for the agency. "We have an inadequate professional milieu in which top flight scientists could come and remain, and remain stimulated and excited by what they do for a longer period of time," he said.

Among the factors contributing to keeping good professionals away was the low salary level and poor physical surroundings, and "doing research on other people's research," Commissioner Schmidt said. Nevertheless, Dr. Schmidt hailed the work done by the FDA professional staff. "They make decisions which are sometimes literally life and death decisions for large numbers of people. I am constantly amazed that we do have top notch people in the agency who are happy and productive."

Dr. Schmidt pointed out that "We do not actively license researchers," when Dr. Sackler asked if the agency has a right to license physicians to do research. "We can defrock them for fraudulent research," said Dr. Schmidt.

Next week's installment will cover Dr. Schmidt's comments on physicians' use of the package insert and misunderstandings about the FDA agency, the role of practicing physicians in FDA decision-making, the relationship of the malpractice crisis to FDA regulations and drug liability.

Arthritic Women May Benefit from Hormone Therapy

Continued from page 2

upper respiratory infections or other disorders not related to their primary disease.

Other laboratory changes are similar to those found with the uses of female hormones and oral contraceptives in other conditions, Dr. Varon noted. Toxicity, which in turn, might have required changing the regimen, has not occurred. In contrast to therapy with adrenal steroids, high dose sex hormone treatment is not only anti-inflammatory but also anabolic.

Dr. Varon emphasized that the high dose sex hormone injections did not have to be stopped in a single patient because of poor tolerance. All patients noted improvements in attitudes and feelings of well-being. Women who described marked general reduction in energy prior to treatment frequently required less bedrest after treatment. As a result, they wanted to lead more active lives and increased mobility helped speed up total rehabilitation.

Concludes Dr. Varon: High dose sex hormones may be given at any stage of the pyramidal plan for management of rheumatoid arthritis as part of a basic program along with heat and aspirin. It may also be valuable therapy in advanced cases where reconstructive surgery, rehabilitation, or experimental treatment are considered.

Collaborators with Dr. Varon in the study were Dr. Robert H. Millwee of Dallas and Dr. James W. Finney of Fort Worth.

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INDICATIONS
Hypertension and edema.

CONTRAINDICATIONS
Anuria; hypersensitivity to this or other sulfonamide-derived drugs. The routine use of diuretics in an otherwise healthy pregnant woman with or without mild edema is contraindicated and possibly hazardous.

WARNINGS
Use with caution in severe renal disease. In patients with renal disease, thiazides may precipitate azotemia. Cumulative effects of the drug may develop in patients with impaired renal function.

Thiazides should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte imbalance may precipitate hepatic coma.

Thiazides may be additive or potentiative of the action of other antihypertensive drugs. Potentiation occurs with ganglionic or peripheral adrenergic blocking drugs.

Sensitivity reactions are more likely to occur in patients with a history of allergy or bronchial asthma.

The possibility of exacerbation or activation of systemic lupus erythematosus has been reported.

Usage in Pregnancy
Use of thiazides in women of childbearing age requires that the potential benefits of the drug be weighed against its possible hazards to the fetus. These hazards include fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions which have occurred in the adult.

Nursing Mothers
Thiazides cross the placental barrier and appear in cord blood and breast milk.

PRECAUTIONS
Periodic determination of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals. Observe patients for clinical signs of fluid or electrolyte imbalance (hyponatremia, hypochloremic alkalosis, and hypokalemia). Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Medication such as digitalis may also influence serum electrolytes. Warning signs are dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbance such as nausea or vomiting.

Hypokalemia may develop with thiazides as with any other potent diuretic, especially during brisk diuresis, when severe cirrhosis is present, or during concomitant administration of steroids or ACTH.

Interference with adequate oral intake of electrolytes will also contribute to hypokalemia. Digitalis therapy may exaggerate metabolic effects of hypokalemia especially with reference to myocardial activity.

Any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease). Dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy is water restriction rather than administration of salt, except in rare instances when the hyponatremia is life-threatening. In actual salt depletion, appropriate replacement is the therapy of choice.

Translant elevations in plasma calcium may occur in patients receiving thiazides, particularly in those with hyperparathyroidism. Pathological changes in the parathyroid gland have been reported in a few patients on prolonged thiazide therapy.

Hyperuricemia may occur or frank gout may be precipitated in certain patients. Insulin requirements in diabetic patients may be increased, decreased, or unchanged. Latent diabetes may become manifest during thiazide administration.

Thiazide drugs may increase the responsiveness to tubocurarine. The antihypertensive effects of the drug may be enhanced in the post-sympathectomy patient. Thiazides may decrease arterial responsiveness to norepinephrine. This is not sufficient to preclude effectiveness of the pressor agent for therapeutic use.

If nitrogen retention indicates onset of progressive renal impairment, consider withholding or discontinuing diuretic therapy.

Thiazides may decrease serum PBI levels without signs of thyroid disturbance.

ADVERSE REACTIONS
Gastrointestinal—anorexia, gastric irritation, nausea, vomiting, cramping, diarrhea, constipation, jaundice (intrahepatic cholestatic), pancreatitis.
Central Nervous System—dizziness, vertigo, paresthesias, headache, xanthopsia. *Dermatologic-hypersensitivity*—purpura, photosensitivity, rash, urticaria, necrotizing angiitis, Stevens-Johnson syndrome, and other hypersensitivity reactions.
Hematologic—leukopenia, agranulocytosis, thrombocytopenia, aplastic anemia. *Cardiovascular*—orthostatic hypotension may occur and may be potentiated by alcohol, barbiturates, or narcotics. *Other*—hyperglycemia, glycosuria, hyperuricemia, muscle spasm, weakness, restlessness. Whenever adverse reactions are moderate or severe, reduce dosage or withdraw therapy.

DOSAGE
Individualize dosage by titrating for maximum therapeutic response at the lowest possible dose.

Hypertension: Initial—Usual dose 25 mg daily. *Maintenance*—After a week dosage may be adjusted downward to as little as 25 mg or upward to as much as 100 mg daily. *Combined therapy*—When necessary, other antihypertensives may be added gradually and with caution because of the potentiating effect of this drug. Dosages of ganglionic blockers should be halved.

Edema: Initial—25 to 200 mg daily for several days. *Maintenance*—25 to 100 mg daily or intermittently. Refractory patients may require up to 200 mg daily.

SUPPLIED
Tablets, 50 mg (yellow, scored), bottles of 30, 60, 100, 1000, 5000, and Accupak blister units of 100. Tablets, 25 mg (pink, scored), bottles of 30, 60, 100, 1000 and 5000.

Consult complete literature before prescribing.

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